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Subject: RE: 09/187,693

m.c

Please deliver the following references:

J Cell Biol 116(2): 321-30; 1992

International J. of Oncology 13(2): 335-42; Aug 1998

International J. of Oncology 10(2): 339-347

J. of cellular biochemistry 51(2): 236-48

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in Derwent Patent Files
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L1 2131067 ANTIBODY

4 FILES SEARCHED...

=> s 12 and EGFR

=> s 12 and EGFR

=> s 14 and tyrosine phosphorylation

=> s 15 and inhibit

=> s 16 and internalization

=> s 16 and degradation

$\Rightarrow d \mid 18$ all

TI Protein kinase C **inhibits epidermal growth factor receptor** phosphorylation in enterocytes
 AU Summers S T (Reprint); Bass B L
 CS VET ADM MED CTR, DEPT SURG, BALTIMORE, MD 21201 (Reprint); UNIV MARYLAND, SCH MED, BALTIMORE, MD 21201
 CYA USA
 SO JOURNAL OF SURGICAL RESEARCH, (APR 1997) Vol. 69, No. 1, pp. 208-211. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0022-4804.
 DT Article; Journal
 FS LIFE
 LA English
 REC Reference Count: 20

AB Epidermal growth factor (EGF) is an important proliferative signal in the gastrointestinal tract. The EGF receptor (**EGFr**), which transduces the mitogenic stimulus to the cell, may be regulated by a number of factors including extracellular matrix, cell-cell contact, and other peptides. As protein kinase C (PK-C) has been shown to phosphorylate

and down-regulate the **EGFr** in certain tumor cell lines, we propose that PK-C, an important regulatory enzyme, modulates the phosphorylation of the **EGFr** in the IEC 6 rat enterocyte cell line. IEC 6 cells were cultured in dishes with Dulbecco's modified Eagle's

medium, (DMEM)/5% fetal bovine serum (FBS), which was changed to DMEM/1% FBS 24 in prior to all experiments. Cells (three dishes per group) were treated with the PK-C activating phorbol ester phorbol-12-myristate-13-acetate (PMA) (100 nM) or vehicle for 1 hr and challenged with EGF (50 ng/ml) or vehicle for 15 min. Cell lysates were then prepared **EGFr tyrosine phosphorylation** was determined by immunoprecipitating the **EGFr** and immunoblotting with an **antibody** against phosphotyrosine, **EGFr** apparent molecular weight was assessed in the same lysates by Western blot with an anti-**EGFr antibody**. Blots were analyzed by computer densitometry. Data are expressed as mean +/- SEM; n = 3 with P value determined by t test. Exposure of cells to PMA resulted in a decrease in the EGF-stimulated **EGFr** phosphotyrosine content from 96 +/- 5 U in control to 66 +/- 6 U in PMA (P < 0.01). The amount of receptor did

not change, 43 +/- 3 U in control vs 44 +/- 3 U in PMA (P = 0.44). Further, exposure to PMA in the absence of EGF caused a gel shift of the **EGFr** band consistent with a nontyrosine phosphorylation of the protein. We demonstrate that activation of PKC results in a modification of the **EGFr** coincident with inhibition of EGF-stimulated receptor tyrosine kinase activity. These data support a role for PK-C in the regulation of **EGFr** function and hence modulation of mitogenic signals

in enterocytes. (C) 1997 Academic Press.

CC SURGERY
 STP KeyWords Plus (R): INTESTINAL EPITHELIAL-CELLS; RAT SMALL-INTESTINE; PROLIFERATION; **DEGRADATION**; EXPRESSION

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
BALIGA B S	1989	19	1045	BIOCHEM INT
BERNARD J A	1995	108	564	GASTROENTEROLOGY

BJORGE J D	1987	262	6615	J BIOL CHEM
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KEGEL M	1982	113	125	J CELL PHYSIOL
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POLK D B	1994	107	109	GASTROENTEROLOGY
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SEEDORF K	1995	270	18953	J BIOL CHEM
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WOLPERT S I	1996	171	109	AM J SURG
WOLPERT S I	1996	63	345	J SURG RES

=> d his

(FILE 'HOME' ENTERED AT 11:33:30 ON 27 FEB 2001)

FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:33:51 ON 27 FEB 2001

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L1      2131067 S ANTIBODY
L2      7067 S L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR
L3      2494 S L2 AND EGFR
L4      2494 S L2 AND EGFR
L5      187 S L4 AND TYROSINE PHOSPHORYLATION
L6      30 S L5 AND INHIBIT
L7      0 S L6 AND INTERNALIZATION
L8      1 S L6 AND DEGRADATION

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=> s l5 and KD

L9 6 L5 AND KD

=> d l9 all 1-6

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L9      ANSWER 1 OF 6 MEDLINE
AN      1999194218 MEDLINE
DN      99194218
TI      Eradication of established tumors by a fully human monoclonal
        antibody to the epidermal growth
        factor receptor without concomitant chemotherapy.
AU      Yang X D; Jia X C; Corvalan J R; Wang P; Davis C G; Jakobovits A
CS      Abgenix, Inc., Fremont, California 94555, USA.. yang_xd@abgenix.com
SO      CANCER RESEARCH, (1999 Mar 15) 59 (6) 1236-43.
        Journal code: CNF. ISSN: 0008-5472.
CY      United States
DT      Journal; Article; (JOURNAL ARTICLE)
LA      English
FS      Priority Journals; Cancer Journals
EM      199906

```

AB A fully human IgG2kappa monoclonal **antibody** (MAb), E7.6.3, specific to the human epidermal growth factor (EGF) receptor (**EGFr**) was generated from human **antibody**-producing XenoMouse strains engineered to be deficient in mouse **antibody** production and to contain the majority of the human **antibody** gene repertoire on megabase-sized fragments from the human heavy and kappa light chain loci. The E7.6.3 MAb exhibits high affinity ($KD = 5 \times 10^{-11}$ M) to the receptor, blocks completely the binding of both EGF and transforming growth factor alpha (TGF- α) to various **EGFr**-expressing human carcinoma cell lines, and abolishes EGF-dependent cell activation, including **EGFr tyrosine phosphorylation**, increased extracellular acidification rate, and cell proliferation. The **antibody** (0.2 mg i.p. twice a week for 3 weeks) prevents completely the formation of human epidermoid carcinoma A431 xenografts in athymic mice. More importantly, the administration of E7.6.3 without concomitant chemotherapy results in complete eradication of established tumors as large as 1.2 cm³. Tumor eradication of A431 xenografts was achieved in nearly all of the mice treated with total E7.6.3 doses as low as 3 mg, administered over the course of 3 weeks, and a total dose of 0.6 mg led to tumor elimination in 65% of the mice. No tumor recurrence was observed for more than 8 months after the last **antibody** injection, which further indicated complete tumor cell elimination by the **antibody**. The potency of E7.6.3 in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for the treatment of multiple **EGFr**-expressing human solid tumors, including those for which no effective chemotherapy is available. Being a fully human **antibody**, E7.6.3 is expected to exhibit minimal immunogenicity and a longer half-life as compared with mouse or mouse-derivatized MAbs, thus allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

CT Check Tags: Animal; Human; Male
***Antibodies, Monoclonal: TU, therapeutic use**
Antibody Affinity
***IgG: TU, therapeutic use**
 Immunotherapy
 Mice
 Mice, Inbred BALB C
 Mice, Nude
 Neoplasm Transplantation
 Neoplasms, Experimental: PA, pathology
 Neoplasms, Experimental: PC, prevention & control
***Neoplasms, Experimental: TH, therapy**
***Receptor, Epidermal Growth Factor: IM, immunology**
 Transplantation, Heterologous

CN EC 2.7.11.- (Receptor, Epidermal Growth Factor); 0 (**Antibodies, Monoclonal**); 0. (IgG)

L9 ANSWER 2 OF 6 MEDLINE
 AN 95032035 MEDLINE
 DN 95032035
 TI Nuclear localization of p185neu tyrosine kinase and its association with transcriptional transactivation.
 AU Xie Y; Hung M C
 CS Department of Tumor Biology, University of Texas M. D. Anderson Cancer

Center, Houston 77030.

NC CA58880 (NCI)
CA60856 (NCI)

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Sep 30) 203
(3) 1589-98.
Journal code: 9Y8. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199501

AB The rat neu protooncogene encodes a 185 kD transmembrane protein (p185neu), which is a member of the **epidermal growth factor receptor (EGFr)** family. In searching for the signaling transducer of p185neu by using a two-hybrid selection system, we found, surprisingly, that the cytoplasmic domain of p185neu, when fused to the DNA-binding domain of GAL4 (amino acids 1-147), functioned as a transcriptional activator. We subsequently observed nuclear localization of p185neu. Interestingly, nuclear p185neu has a much higher extent of **tyrosine phosphorylation** than its nonnuclear counterpart. Our results suggest that a transmembrane receptor tyrosine kinase may enter the nucleus and be involved in transcriptional activation. This novel finding unveils a clue in the understanding of the mechanism of receptor tyrosine kinase-mediated signal transduction.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S. Cell Line
*Cell Nucleus: ME, metabolism
Fluorescent Antibody Technique
Fungal Proteins: BI, biosynthesis
Fungal Proteins: ME, metabolism
*Gene Expression Regulation
*Genes, erbB-2
Plasmids
Promoter Regions (Genetics)
Protein-Tyrosine Kinase: AN, analysis
Protein-Tyrosine Kinase: BI, biosynthesis
*Protein-Tyrosine Kinase: ME, metabolism
Rats
Receptor, erbB-2: AN, analysis
Receptor, erbB-2: BI, biosynthesis
*Receptor, erbB-2: ME, metabolism
Recombinant Fusion Proteins: AN, analysis
Recombinant Fusion Proteins: ME, metabolism
Saccharomyces cerevisiae: GE, genetics
Saccharomyces cerevisiae: ME, metabolism
Sequence Deletion
Signal Transduction
*Transcription, Genetic

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Receptor, erbB-2); 0 (Fungal Proteins); 0 (GAL4 protein, Saccharomyces); 0 (Plasmids); 0 (Recombinant Fusion Proteins)

GEN neu

L9 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:173234 BIOSIS

DN PREV199900173234

TI Eradication of established tumors by a fully human monoclonal **antibody** to the **epidermal growth factor receptor** without concomitant chemotherapy.

AU Yang, Xiao-Dong (1); Jia, Xiao-Chi; Corvalan, Jose R. F.; Wang, Ping; Davis, C. Geoffrey; Jakobovits, Aya

CS (1) Abgenix, Inc., 7601 Dumbarton Circle, Fremont, CA, 94555 USA

SO Cancer Research, (March 15, 1999) Vol. 59, No. 6, pp. 1236-1243. ISSN: 0008-5472.

DT Article

LA English

AB A fully human IgG2kappa monoclonal **antibody** (MAb), E7.6.3, specific to the human epidermal growth factor (EGF) receptor (**EGFr**) was generated from human **antibody**-producing XenoMouse strains engineered to be deficient in mouse **antibody** production and to contain the majority of the human **antibody** gene repertoire on megabase-sized fragments from the human heavy and kappa light chain loci. The E7.6.3 MAb exhibits high affinity ($KD = 5 \times 10^{-11}$ M) to the receptor, blocks completely the binding of both EGF and transforming growth factor alpha (TGF-alpha) to various **EGFr**-expressing human carcinoma cell lines, and abolishes EGF-dependent cell activation, including **EGFr tyrosine phosphorylation**, increased extracellular acidification rate, and cell proliferation. The **antibody** (0.2 mg i.p. twice a week for 3 weeks) prevents completely the formation of human epidermoid carcinoma A431 xenografts in athymic mice. More importantly, the administration of E7.6.3 without concomitant chemotherapy results in complete eradication of established tumors as large as 1.2 cm³. Tumor eradication of A431 xenografts was achieved in nearly all of the mice treated with total E7.6.3 doses as low as 3 mg, administered over the course of 3 weeks, and a total dose of 0.6 mg led to tumor elimination in 65% of the mice. No tumor recurrence was observed for more than 8 months after the last **antibody** injection, which further indicated complete tumor cell elimination by the **antibody**. The potency of E7.6.3 in eradicating well-established tumors without concomitant chemotherapy indicates its potential as a monotherapeutic agent for the treatment of multiple **EGFr**-expressing human solid tumors, including those for which no effective chemotherapy is available. Being a fully human **antibody**, E7.6.3 is expected to exhibit minimal immunogenicity and a longer half-life as compared with mouse or mouse-derivatized MABs, thus allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

CC Biochemical Studies - General *10060
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - General *24002

BC Muridae 86375

IT Major Concepts
Biochemistry and Molecular Biophysics; Tumor Biology

IT Diseases
solid tumor: neoplastic disease

IT Chemicals & Biochemicals
human **epidermal growth factor receptor**; transforming growth factor-alpha; E7.6.3: IgG2 kappa monoclonal **antibody**

IT Alternate Indexing
Neoplasms (MeSH)

IT Methods & Equipment
 chemotherapy: therapeutic method

IT Miscellaneous Descriptors
 treatment development

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 XenoMouse (Muridae): animal model

ORGN Organism Superterms
 Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
 Rodents; Vertebrates

L9 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS

AN 1999:193266 CAPLUS

DN 130:350943

TI Eradication of established tumors by a fully human monoclonal
antibody to the **epidermal growth**
factor receptor without concomitant chemotherapy

AU Yang, Xiao-Dong; Jia, Xiao-Chi; Corvalan, Jose R. F.; Wang, Ping; Davis,
 C. Geoffrey; Jakobovits, Aya

CS Abgenix, Inc., Fremont, CA, 94555, USA

SO Cancer Res. (1999), 59(6), 1236-1243
 CODEN: CNREA8; ISSN: 0008-5472

PB AACR Subscription Office

DT Journal

LA English

CC 15-3 (Immunochemistry)

AB A fully human IgG2.kappa. monoclonal **antibody** (MAb), E7.6.3,
 specific to the human epidermal growth factor (EGF) receptor (**EGFr**
) was generated from human **antibody**-producing XenoMouse strains
 engineered to be deficient in mouse **antibody** prodn. and to
 contain the majority of the human **antibody** gene repertoire on
 megabase-sized fragments from the human heavy and .kappa. light chain
 loci. The E7.6.3 MAb exhibits high affinity (**KD** = 5.times.10⁻¹¹
 M) to the receptor, blocks completely the binding of both EGF and
 transforming growth factor .alpha. (TGF-.alpha.) to various **EGFr**
 -expressing human carcinoma cell lines, and abolishes EGF-dependent cell
 activation, including **EGFr tyrosine**
phosphorylation, increased extracellular acidification rate, and
 cell proliferation. The **antibody** (0.2 mg i.p. twice a week for
 3 wk) prevents completely the formation of human epidermoid carcinoma

A431 xenografts in athymic mice. More importantly, the administration of
 E7.6.3 without concomitant chemotherapy results in complete eradication
 of established tumors as large as 1.2 cm³. Tumor eradication of A431
 xenografts was achieved in nearly all of the mice treated with total
 E7.6.3 doses as low as 3 mg, administered over the course of 3 wk, and a
 total dose of 0.6 mg led to tumor elimination in 65% of the mice. No
 tumor recurrence was obsd. for more than 8 mo after the last
antibody injection, which further indicated complete tumor cell
 elimination by the **antibody**. The potency of E7.6.3 in
 eradicating well-established tumors without concomitant chemotherapy
 indicates its potential as a monotherapeutic agent for the treatment of
 multiple **EGFr**-expressing human solid tumors, including those for
 which no effective chemotherapy is available. Being a fully human
antibody, E7.6.3 is expected to exhibit minimal immunogenicity and
 a longer half-life as compared with mouse or mouse-derivatized MABs, thus

allowing repeated **antibody** administration, including in immunocompetent patients. These results suggest E7.6.3 as a good candidate for assessing the full therapeutic potential of anti-**EGFr antibody** in the therapy of multiple patient populations with **EGFr**-expressing solid tumors.

ST antitumor monoclonal **antibody** EGF receptor

IT Monoclonal immunoglobulins
 RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
 (IgG2, E7.6.3; antitumor activity of human monoclonal **antibody** to EGF receptor)

IT **Epidermal growth factor receptors**
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (antitumor activity of human monoclonal **antibody** to)

IT Receptor phosphorylation
 (by EGF receptor is prevented by human monoclonal **antibody**)

IT Antitumor agents
 (human monoclonal **antibody** to EGF receptor in relation to)

IT Transforming growth factor .alpha.
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (human monoclonal **antibody** to EGF receptor prevents binding by)

IT Breast carcinoma
 (human monoclonal **antibody** to EGF receptor prevents proliferation of)

IT Cell proliferation
 (human monoclonal **antibody** to EGF receptor prevents proliferation of breast carcinoma cells)

IT Cell activation
 (human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of vulvar carcinoma cells)

IT IgG2
 RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
 (monoclonal, E7.6.3; antitumor activity of human monoclonal **antibody** to EGF receptor)

IT Female reproductive organ
 (vulva, carcinoma; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT Reproductive tract diseases
 (vulvar carcinoma; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT Carcinoma
 (vulvar; human monoclonal **antibody** to EGF receptor prevents receptor-mediated activation of)

IT 79079-06-4, **Epidermal growth factor receptor kinase**
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (antitumor activity of human monoclonal **antibody** to)

RE.CNT 33

RE

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L9 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS

AN 1996:71580 CAPLUS

DN 124:114575

TI Isolated polypeptide erbB-3, related to the **epidermal growth factor receptor** and **antibody** thereto

IN Kraus, Matthias H.; Aaronson, Stuart A.

PA United States Dept. of Health and Human Services, USA

SO U.S., 41 pp. Cont.-in-part of U.S. 5,183,884.

CODEN: USXXAM

DT Patent

LA English

IC ICM C07K004-12

ICS C07K005-04; C07K014-71; C07K016-18

NCL 530326000

CC 14-1 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 15

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5480968	A	19960102	US 1992-978895	19921110
	US 444406	A0	19910315	US 1989-444406	19891201
	US 5183884	A	19930202		
	US 5820859	A	19981013	US 1995-473119	19950607
	US 5916755	A	19990629	US 1995-475352	19950607
PRAI	US 1989-444406		19891201		
	US 1992-978895		19921110		

AB A DNA fragment distinct from the **epidermal growth factor receptor (EGFR)** and erbB-2 genes was detected by reduced stringency hybridization of v-erbB to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region

of v-erbB homol. to three exons with closest homol. of 64% and 67% to a contiguous region within the tyrosine kinase domains of the **EGFR** and erbB-2 proteins, resp. cDNA cloning revealed a predicted 148 kd transmembrane polypeptide with structural features identifying it as a member of the erbB family, prompting designation of the new gene as erbB-3. It was mapped to human chromosome 12 q11-13 and was shown to be expressed as a 6.2 kb transcript in a variety of normal tissues of epithelial origin. Markedly elevated erbB-3 mRNA levels were demonstrated in certain human mammary tumor cell lines. These findings indicate that increased erbB-3 expression, as in the case of **EGFR** and erbB-2, plays a role in some human malignancies. Using erbB-3 specific **antibodies** (polyclonal or monoclonal), the erbB-3 protein was identified as a 180 kDa glycoprotein, gp180EGFR/erbB-3. The intrinsic catalytic function of gp180erbB-3 was uncovered by its ability to autophosphorylate in vitro. Ligand-dependent signaling of its cytoplasmic domain was established employing transfectants which express a chimeric **EGFR/erbB-3** protein, gp180EGFR/erbB-3. EGF induced **tyrosine phosphorylation** of the chimera and promoted soft agar colony formation of such transfectants. These findings, combined with the detection of constitutive **tyrosine phosphorylation** of gp180erbB-3 in 4 out of 12 human mammary tumor cell lines, implicate the activated erbB-3 product in the pathogenesis of some human malignancies.

ST erbB3 gp180 malignancy
IT Cytotoxic agents
(conjugate with anti-gp180EGFR/erbB-3 **antibody**; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Peptides, biological studies
Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gp180EGFR/erbB-3-contg.; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Receptors
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Neoplasm
Neoplasm inhibitors
Protein sequences
(isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Gene, animal
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(c-erbB3, protein; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Deoxyribonucleic acid sequences
(complementary, isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Receptors
RL: PRP (Properties)
(gene c-erbB3, isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT Glycoproteins, specific or class
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(gp180, gp180EGFR/erbB-3; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173147-30-3, Receptor (human clone pE3 gene c-erbB3)
RL: PRP (Properties)
(amino acid sequence; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 147014-95-7, C-ErbB-3 protein kinase
RL: PRP (Properties)
(isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173147-29-0
RL: PRP (Properties)
(nucleotide sequence; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

IT 173073-14-8P 173073-15-9P 173073-16-0P 173073-17-1P 173073-18-2P
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polypeptide contg.; isolation and characterization of erbB-3/gp180 gene and gene product and **antibody** and cytotoxic agent conjugate for diagnosis and therapy of cancer)

L9 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1992:52332 CAPLUS
DN 116:52332
TI Association of the tyrosine phosphorylated **epidermal growth factor receptor** with a 55-kD tyrosine phosphorylated protein at the cell surface and in endosomes
AU Wada, Ikuo; Lai, Wei H.; Posner, Barry I.; Bergeron, John J. M.
CS Dep. Anat., McGill Univ., Montreal, PQ, H3A 2B2, Can.
SO J. Cell Biol. (1992), 116(2), 321-30
CODEN: JCLBA3; ISSN: 0021-9525
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB After the intraportal injection of EGF, the EGF receptor (**EGFR**) is rapidly internalized into hepatic endosomes where it remains largely receptor bound (Lai W. H., et al., 1989). In the present study, the phosphotyrosine content of **EGFRs** at the cell surface and in

endosomes was evaluated in order to assess the consequences of internalization. Quant. ests. of specific radioactivity of the **EGFR** in these 2 compartments revealed that **tyrosine phosphorylation** of the **EGFR** was obsd. at the cell surface within 30 s of ligand administration. However, the **EGFR** was also highly phosphorylated in endosomes reaching levels of **tyrosine phosphorylation** higher than those of the cell surface receptor at 5 and 15 min after EGF injection. A 55-kDa tyrosine phosphorylated polypeptide (pyp55) was obsd. in assocn. with the **EGFR** at the cell surface within 30 s of EGF injection. The protein was also found in assocn. with the **EGFR** in endosomes as evidenced by copptn. studies using a monoclonal **antibody** to the **EGFR** as well as by coelution with the EGR in gel permeation chromatog. Limited proteolysis of isolated endosomes indicated that the tyrosine phosphorylated domains of the **EGFR** and assocd. pyp55 were cytosolically oriented while internalized EGF was intraluminal. The identification of pyp55 in assocn. with **EGFR** in both hepatic plasma membranes and endosomes may be relevant to **EGFR** function and/or trafficking of the **EGFR**.

- ST EGF receptor **tyrosine phosphorylation** internalization;
endosome EGF receptor **tyrosine phosphorylation**;
membrane EGF receptor **tyrosine phosphorylation**
- IT Cell membrane
(EGF receptors of, phosphotyrosine of, of liver, endosome receptors in relation to)
- IT Liver, composition
(EGF receptors of, **tyrosine phosphorylation** of, internalization in relation to)
- IT Phosphorylation, biological
(of tyrosine, of EGF receptors in liver, internalization in relation to)
- IT Organelle
(endocytic vesicle, EGF receptors of, phosphotyrosine of, of liver, cell membrane receptors in relation to)
- IT Receptors
RL: BIOL (Biological study)
(epidermal growth factor, **tyrosine phosphorylation** of, of liver, internalization in relation to)
- IT Biological transport
(internalization, of EGF receptors, in liver, **tyrosine phosphorylation** in relation to)
- IT Phosphoproteins
RL: BIOL (Biological study)
(phosphotyrosine-contg., 55,000-mol.-wt., EGF receptor assocn. with, in cell membrane and endosome of hepatocyte, receptor **tyrosine phosphorylation** at internalization in relation to)
- IT 62229-50-9D, EGF, receptor complexes
RL: PROC (Process)
(internalization of, in liver, **tyrosine phosphorylation** in relation to)
- IT 60-18-4, Tyrosine, biological studies
RL: BIOL (Biological study)
(phosphorylation of, of EGF receptor in liver, internalization in relation to)
- IT 62229-50-9, EGF
RL: BIOL (Biological study)
(receptors for, **tyrosine phosphorylation** of, in

liver, internalization in relation to)

=> d his

(FILE 'HOME' ENTERED AT 11:33:30 ON 27 FEB 2001)

FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:33:51 ON 27 FEB 2001

L1 2131067 S ANTIBODY
L2 7067 S L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR
L3 2494 S L2 AND EGFR
L4 2494 S L2 AND EGFR
L5 187 S L4 AND TYROSINE PHOSPHORYLATION
L6 30 S L5 AND INHIBIT
L7 0 S L6 AND INTERNALIZATION
L8 1 S L6 AND DEGRADATION
L9 6 S L5 AND KD

=> s l5 and threonine phosphorylation

L10 0 L5 AND THREONINE PHOSPHORYLATION

=> s l4 and threonine phosphorylation

L11 0 L4 AND THREONINE PHOSPHORYLATION

=> dup remove l5

PROCESSING COMPLETED FOR L5

L12 73 DUP REMOVE L5 (114 DUPLICATES REMOVED)

=> s l12 and 63

L13 0 L12 AND 63

=> s l13 and 63 Kd

L14 0 L13 AND 63 KD

=> d l12 1-73

L12 ANSWER 1 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 2001:73051 BIOSIS
DN PREV200100073051
TI **Epidermal growth factor receptor**
mediates stress-induced expression of its ligands in rat gastric
epithelial cells.
AU Miyazaki, Yoshiji (1); Hiraoka, Shintaro; Tsutsui, Syusaku; Kitamura,
Shinji; Shinomura, Yasuhisa; Matsuzawa, Yuji
CS (1) Department of Internal Medicine and Molecular Sciences, B5, Graduate
School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871:
miyazaki@imed2.med.osaka-u.ac.jp Japan
SO Gastroenterology, (January, 2001) Vol. 120, No. 1, pp. 108-116. print.
ISSN: 0016-5085.
DT Article

LA English
SL English

L12 ANSWER 2 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 2001:70603 BIOSIS
DN PREV200100070603
TI Stimulation of the mitogen-activated protein kinase cascade and
**tyrosine phosphorylation of the epidermal
growth factor receptor** by hepatopoietin.
AU Li, Yong; Li, Ming; Xing, Guichun; Hu, Zhiyuan; Wang, Qingming; Dong,
Chunna; Wei, Handong; Fan, Guocai; Chen, Jizhong; Yang, Xiaoming; Zhao,
Shifu; Chen, Huipeng; Guan, Kunliang; Wu, Chutse; Zhang, Chenggang; He,
Fuchu (1)
CS (1) Beijing Institute of Radiation Medicine, 27 Taiping Rd., Beijing,
100850: hefc@nic.bmi.ac.cn China
SO Journal of Biological Chemistry, (December 1, 2000) Vol. 275, No. 48, pp..
37443-37447. print.
ISSN: 0021-9258.
DT Article
LA English
SL English

L12 ANSWER 3 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:310879 SCISEARCH
GA The Genuine Article (R) Number: 304WU
TI Cross-talk between **epidermal growth factor
receptor** and c-Met signal pathways in transformed cells
AU Jo M J; Stolz D B; Esplen J E; Dorko K; Michalopoulos G K; Strom S C
(Reprint)
CS UNIV PITTSBURGH, SCH MED, DEPT PATHOL, 200 LOTHROP ST, BST S-450,
PITTSBURGH, PA 15261 (Reprint); UNIV PITTSBURGH, SCH MED, DEPT PATHOL,
PITTSBURGH, PA 15261; UNIV PITTSBURGH, SCH MED, DEPT PHYSIOL & CELL BIOL,
PITTSBURGH, PA 15261
CYA USA
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (24 MAR 2000) Vol. 275, No. 12, pp..
8806-8811.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE
PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 4 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:528191 SCISEARCH
GA The Genuine Article (R) Number: 331XB
TI Integrin alpha 2 beta 1-dependent EGF receptor activation at cell-cell
contact sites
AU Yu X; Miyamoto S; Mekada E (Reprint)
CS OSAKA UNIV, MICROBIAL DIS RES INST, DEPT CELL BIOL, 3-1 YAMADAOKA, SUITA,
OSAKA 5650871, JAPAN (Reprint); KURUME UNIV, INST LIFE SCI, FUKUOKA
8390861, JAPAN; KURUME UNIV, RES CTR INNOVAT CANC THERAPY, FUKUOKA
8390861, JAPAN; KYUSHU NATL CANC CTR, GYNECOL SERV, MINAMI KU, FUKUOKA
8111395, JAPAN
CYA JAPAN
SO JOURNAL OF CELL SCIENCE, (JUN 2000) Vol. 113, No. 12, pp. 2139-2147.

Publisher: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE
COMMERCIAL

PARK COWLEY RD, CAMBRIDGE CB4 4DL, CAMBS, ENGLAND.

ISSN: 0021-9533.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 5 OF 73 MEDLINE DUPLICATE 3

AN 2000473231 MEDLINE

DN 20444296

TI Lysophosphatidic acid inhibits Ca²⁺ signaling in response to
epidermal growth factor receptor
stimulation in human astrocytoma cells by a mechanism involving
phospholipase C(gamma) and a G(alphai) protein.

AU Hernandez M; Barrero M J; Crespo M S; Nieto M L

CS Instituto de Biologia y Genetica Molecular, CSIC-Universidad de
Valladolid, Valladolid, Spain.

SO JOURNAL OF NEUROCHEMISTRY, (2000 Oct) 75 (4) 1575-82.

Journal code: JAV. ISSN: 0022-3042.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200012

EW 20001202

L12 ANSWER 6 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 4

AN 2000:939453 SCISEARCH

GA The Genuine Article (R) Number: 380WL

TI Cellular signaling by **tyrosine phosphorylation** in
keloid and normal human dermal fibroblasts

AU Chin G S; Liu W; Steinbrech D; Hsu M; Levinson H; Longaker M T (Reprint)

CS STANFORD UNIV, SCH MED, DEPT SURG, H3680, 300 PASTEUR DR, STANFORD, CA
94305 (Reprint); NYU, MED CTR, DEPT SURG, LAB DEV BIOL & REPAIR, NEW
YORK,

NY 10016

CYA USA

SO PLASTIC AND RECONSTRUCTIVE SURGERY, (DEC 2000) Vol. 106, No. 7, pp.
1532-1540.

Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA
19106-3621.

ISSN: 0032-1052.

DT Article; Journal

FS LIFE; CLIN

LA English

REC Reference Count: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 7 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 2001016690 EMBASE

TI Critical role of extracellular signal-regulated kinase (ERK)
phosphorylation in novel vitamin K analog-induced cell death.

AU Osada S.; Carr B.I.

CS S. Osada, Department of Surgery, Thomas E. Starzl Transplant. Inst.,
University of Pittsburgh, Pittsburgh, PA 15213, United States.

CYPO5471@nifty.ne.jp

SO Japanese Journal of Cancer Research, (2000) 91/12 (1250-1257).
 Refs: 32
 ISSN: 0910-5050 CODEN: JJCREP

CY Japan
 DT Journal; Article
 FS 016 Cancer
 029 Clinical Biochemistry
 030 Pharmacology
 037 Drug Literature Index
 048 Gastroenterology

LA English
 SL English

L12 ANSWER 8 OF 73 MEDLINE DUPLICATE 5
 AN 2000131152 MEDLINE
 DN 20131152
 TI Mechanical stretch stimulates growth of vascular smooth muscle cells via **epidermal growth factor receptor**.
 AU Iwasaki H; Eguchi S; Ueno H; Marumo F; Hirata Y
 CS Division of Endocrinology and Metabolism, Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo 113-8519, Japan.
 SO Am J Physiol Heart Circ Physiol, (2000 Feb) 278 (2) H521-9.
 Journal code: DKM. ISSN: 0363-6135.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200005
 EW 20000501

L12 ANSWER 9 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6
 AN 2000:347836 BIOSIS
 DN PREV200000347836
 TI Tri-iodothyronine induces proliferation in cultured bovine thyroid cells: Evidence for the involvement of epidermal growth factor-associated tyrosine kinase activity.
 AU Di Fulvio, M. (1); Coleoni, A. H.; Pellizas, C. G.; Masini-Repiso, A. M.
 CS (1) Departamento de Bioquimica Clinica, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Ciudad Universitaria, 5000, Cordoba Argentina
 SO Journal of Endocrinology, (July, 2000) Vol. 166, No. 1, pp. 173-182. print.
 ISSN: 0022-0795.
 DT Article
 LA English
 SL English

L12 ANSWER 10 OF 73 MEDLINE DUPLICATE 7
 AN 2000078900 MEDLINE
 DN 20078900
 TI Ratiometric assay of **epidermal growth factor receptor** tyrosine kinase activation.
 AU Schooler K; Wiley H S
 CS Division of Cell Biology, University of Utah, Salt Lake City, Utah, 84132, USA.
 SO ANALYTICAL BIOCHEMISTRY, (2000 Jan 1) 277 (1) 135-42.

Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200006
EW 20000604

L12 ANSWER 11 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 8
AN 2001:59031 BIOSIS
DN PREV200100059031
TI Enhanced apoptosis with combination C225/radiation treatment serves as
the

impetus for clinical investigation in head and neck cancers.

AU Bonner, James A. (1); Raisch, Kevin P.; Trummell, Hoa Q.; Robert, Francisco; Meredith, Ruby F.; Spencer, Sharon A.; Buchsbaum, Donald J.; Saleh, Mansoor N.; Stackhouse, Murray A.; LoBuglio, Albert F.; Peters, Glenn E.; Carroll, William R.; Waksal, Harlan W.

CS (1) Department of Radiation Oncology, University of Alabama at Birmingham,

1530 3rd Ave South, WTI 105, Birmingham, AL, 35294-3300 USA

SO Journal of Clinical Oncology, (November 1, 2000) Vol. 18, No. 21
Supplement, pp. 47s-53s. print.
ISSN: 0732-183X.

DT Article
LA English
SL English

L12 ANSWER 12 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 2000:822458 CAPLUS
TI Enhanced apoptosis with combination C225/radiation treatment serves as
the

impetus for clinical investigation in head and neck cancers

AU Bonner, James A.; Raisch, Kevin P.; Trummell, Hoa Q.; Robert, Francisco; Meredith, Ruby F.; Spencer, Sharon A.; Buchsbaum, Donald J.; Saleh, Mansoor N.; Stackhouse, Murray A.; LoBuglio, Albert F.; Peters, Glenn E.; Carroll, William R.; Waksal, Harlan W.

CS Comprehensive Cancer Center (Experimental Therapeutics Program),
University of Alabama at Birmingham, Birmingham, AL, 35294-3300, USA

SO J. Clin. Oncol. (2000), 18(21, Suppl.), 47S-53S
CODEN: JCONDN; ISSN: 0732-183X

PB Lippincott Williams & Wilkins
DT Journal
LA English

RE.CNT 35
RE

(1) Bonner, J; Int J Radiat Oncol Biol Phys 1994, V29, P243 CAPLUS

(2) Bonner, J; Int J Radiat Oncol Biol Phys 1998, V42, P921 CAPLUS

(6) Contessa, J; Clin Cancer Res 1999, V5, P405 CAPLUS

(8) David, M; J Biol Chem 1996, V271, P9185 CAPLUS

(12) Grandis, J; J Clin Invest 1998, V102, P1385 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:12020 SCISEARCH
GA The Genuine Article (R) Number: 267WR
TI Activation of **epidermal growth factor**
receptor promotes late terminal differentiation of cell-matrix

interaction-disrupted keratinocytes

AU Wakita N (Reprint); Takigawa M

CS HAMAMATSU UNIV, SCH MED, DEPT DERMATOL, 3600 HANDA CHO, HAMAMATSU, SHIZUOKA 431319, JAPAN (Reprint)

CYA JAPAN

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (24 DEC 1999) Vol. 274, No. 52, pp. 37285-37291.
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
 ISSN: 0021-9258.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 45
 ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 14 OF 73 MEDLINE DUPLICATE 9

AN 1999214601 MEDLINE

DN 99214601

TI Keratinocyte collagenase-1 expression requires an **epidermal growth factor receptor** autocrine mechanism.

AU Pilcher B K; Dumin J; Schwartz M J; Mast B A; Schultz G S; Parks W C; Welgus H G

CS Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110, USA..
 bpilcher@im.wustl.edu

NC K-01

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 9) 274 (15) 10372-81.
 Journal code: HIV. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199907

L12 ANSWER 15 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 1999:581209 SCISEARCH

GA The Genuine Article (R) Number: 219PQ

TI **Epidermal growth factor receptor**
 internalization rate is regulated by negative charges near the SH2 binding site tyr992

AU Holbrook M R; ODonnell J B; Slakey L L; Gross D J (Reprint)

CS UNIV MASSACHUSETTS, DEPT BIOCHEM & MOL BIOL, PROGRAM MOL & CELLULAR BIOL, LEDERLE GRC, AMHERST, MA 01003 (Reprint); UNIV MASSACHUSETTS, DEPT BIOCHEM & MOL BIOL, PROGRAM MOL & CELLULAR BIOL, AMHERST, MA 01003; UNIV MASSACHUSETTS, COLL NAT SCI & MATH, AMHERST, MA 01003

CYA USA

SO BIOCHEMISTRY, (20 JUL 1999) Vol. 38, No. 29, pp. 9348-9356.
 Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
 ISSN: 0006-2960.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 50
 ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 16 OF 73 MEDLINE DUPLICATE 10
 AN 1999427869 MEDLINE
 DN 99427869
 TI Endothelin-mediated vascular growth requires p42/p44 mitogen-activated protein kinase and p70 S6 kinase cascades via transactivation of **epidermal growth factor receptor**.
 AU Iwasaki H; Eguchi S; Ueno H; Marumo F; Hirata Y
 CS Second Department of Internal Medicine, Tokyo Medical and Dental University, Japan.
 SO ENDOCRINOLOGY, (1999 Oct) 140 (10) 4659-68.
 Journal code: EGZ. ISSN: 0013-7227.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199912

L12 ANSWER 17 OF 73 MEDLINE DUPLICATE 11
 AN 1999365145 MEDLINE
 DN 99365145
 TI Radiation-induced release of transforming growth factor alpha activates the **epidermal growth factor receptor** and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death.
 AU Dent P; Reardon D B; Park J S; Bowers G; Logsdon C; Valerie K; Schmidt-Ullrich R
 CS Department of Radiation Oncology, Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, USA.. PDENT@HSC.VCU.EDU
 NC P01CA72955 (NCI)
 R01CA65896 (NCI)
 SO MOLECULAR BIOLOGY OF THE CELL, (1999 Aug) 10 (8) 2493-506.
 Journal code: BAU. ISSN: 1059-1524.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199912

L12 ANSWER 18 OF 73 MEDLINE DUPLICATE 12
 AN 1999310812 MEDLINE
 DN 99310812
 TI 4-hydroxynonenal triggers an **epidermal growth factor receptor**-linked signal pathway for growth inhibition.
 AU Liu W; Akhand A A; Kato M; Yokoyama I; Miyata T; Kurokawa K; Uchida K; Nakashima I
 CS Department of Immunology, Nagoya University School of Medicine, Showa-ku, Nagoya 466-8550, Japan.
 SO JOURNAL OF CELL SCIENCE, (1999 Jul) 112 (Pt 14) 2409-17.
 Journal code: HNK. ISSN: 0021-9533.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199912

L12 ANSWER 19 OF 73 MEDLINE
AN 1999194218 MEDLINE
DN 99194218
TI Eradication of established tumors by a fully human monoclonal
antibody to the epidermal growth
factor receptor without concomitant chemotherapy.
AU Yang X D; Jia X C; Corvalan J R; Wang P; Davis C G; Jakobovits A
CS Abgenix, Inc., Fremont, California 94555, USA.. yang_xd@abgenix.com
SO CANCER RESEARCH, (1999 Mar 15) 59 (6) 1236-43.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199906

L12 ANSWER 20 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:2954 BIOSIS
DN PREV200000002954
TI Ionizing radiation stimulates existing signal transduction pathways
involving the activation of **epidermal growth**
factor receptor and erbB-3, and changes of intracellular
calcium in A431 human squamous carcinoma cells.
AU Todd, D. G. (1); Mikkelsen, R. B. (1); Rorrer, W. K. (1); Valerie, K.
(1);
Schmidt-Ullrich, R. K. (1)
CS (1) Department of Radiation Oncology, Medical College of
Virginia/Virginia
Commonwealth University, Richmond, VA, 23298-0058 USA
SO Journal of Receptor and Signal Transduction Research, (Nov., 1999) Vol.
19, No. 6, pp. 885-908.
ISSN: 1079-9893.
DT Article
LA English
SL English

L12 ANSWER 21 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:803044 SCISEARCH
GA The Genuine Article (R) Number: 246DW
TI Inhibition of **epidermal growth factor**
receptor-associated tyrosine phosphorylation
in human carcinomas with CP-358,774: Dynamics of receptor inhibition in
situ and antitumor effects in athymic mice
AU Pollack V A (Reprint); Savage D M; Baker D A; Tsaparikos K E; Sloan D E;
Moyer J D; Barbacci E G; Pustilnik L R; Smolarek T A; Davis J A; Vaidya M
P; Arnold L D; Doty J L; Iwata K K; Morin M J
CS PFIZER INC, CENT RES, DEPT GENOM TARGETS & CANC RES, EASTERN POINT RD,
GROTON, CT 06340 (Reprint)
CYA USA
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (NOV 1999) Vol.
291, No. 2, pp. 739-748.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650
ROCKVILLE
PIKE, BETHESDA, MD 20814-3998.
ISSN: 0022-3565.
DT Article; Journal
FS LIFE

LA English
REC Reference Count: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 22 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:112903 BIOSIS
DN PREV199900112903
TI 1,25-Dihydroxyvitamin D3 increases the growth-promoting activity of
autocrine **epidermal growth factor**
receptor ligands in keratinocytes.
AU Garach-Jehoshua, Osnat; Ravid, Amiram; Liberman, Uri A.; Koren, Ruth (1)
CS (1) Felsenstein Med. Res. Cent., Rabin Med. Cent., Beilinson Campus,
Petah
Tikva 49100 Israel
SO Endocrinology, (Feb., 1999) Vol. 140, No. 2, pp. 713-721.
ISSN: 0013-7227.
DT Article
LA English

L12 ANSWER 23 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:192347 SCISEARCH
GA The Genuine Article (R) Number: 172CU
TI Transforming growth factor-alpha short-circuits downregulation of the
epidermal growth factor receptor
AU Ouyang X M; Gulliford T; Huang G C; Epstein R J (Reprint)
CS HAMMERSMITH HOSP, IMPERIAL COLL SCH MED, DEPT METAB MED, ROOM 5S1,
COMMONWEALTH BLDG, DU CANE RD, LONDON W12 ONN, ENGLAND (Reprint);
IMPERIAL
COLL SCH MED, DEPT METAB MED, LONDON, ENGLAND; IMPERIAL COLL SCH MED,
DEPT
ONCOL, LONDON, ENGLAND
CYA ENGLAND
SO JOURNAL OF CELLULAR PHYSIOLOGY, (APR 1999) Vol. 179, No. 1, pp. 52-57.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW
YORK,
NY 10158-0012.
ISSN: 0021-9541.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 24 OF 73 MEDLINE DUPLICATE 14
AN 2000029737 MEDLINE
DN 20029737
TI In vitro endosome-lysosome transfer of dephosphorylated EGF receptor and
Shc in rat liver.
AU Authier F; Chauvet G
CS Institut National de la Sante et de la Recherche Medicale U510, Faculte
de
Pharmacie Paris XI, 5 rue Jean-Baptiste Clement, 92296, Chatenay-Malabry,
France.. francois.authier@cep.u-psud.fr
SO FEBS LETTERS, (1999 Nov 12) 461 (1-2) 25-31.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals; Cancer Journals
EM 200002
EW 20000204

L12 ANSWER 25 OF 73 MEDLINE . DUPLICATE 15
AN 1999041949 MEDLINE
DN 99041949
TI Peroxynitrite induces covalent dimerization of **epidermal growth factor receptors** in A431 epidermoid carcinoma cells.
AU van der Vliet A; Hristova M; Cross C E; Eiserich J P; Goldkorn T
CS Center for Comparative Respiratory Biology and Medicine, Department of Internal Medicine, University of California, Davis, California 95616, USA.
NC HL57452 (NHLBI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Nov 27) 273 (48) 31860-6.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902

L12 ANSWER 26 OF 73 MEDLINE DUPLICATE 16
AN 1998362025 MEDLINE
DN 98362025
TI EAST, an **epidermal growth factor receptor**- and Eps15-associated protein with Src homology 3 and tyrosine-based activation motif domains.
AU Lohi O; Poussu A; Merilainen J; Kellokumpu S; Wasenius V M; Lehto V P
CS Department of Pathology, University of Oulu, Oulu, FIN-90220, Finland.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Aug 14) 273 (33) 21408-15.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-AJ224514
EM 199811

L12 ANSWER 27 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:948401 SCISEARCH
GA The Genuine Article (R) Number: 146NJ
TI Reciprocal interactions between beta 1-integrin and **epidermal growth factor receptor** in three-dimensional basement membrane breast cultures: A different perspective in epithelial biology
AU Wang F; Weaver V M; Petersen O W; Larabell C A; Dedhar S; Briand P; Lupu R; Bissell M J (Reprint)
CS UNIV CALIF BERKELEY, LAWRENCE BERKELEY LAB, DIV LIFE SCI, BERKELEY, CA 94720 (Reprint); UNIV CALIF BERKELEY, LAWRENCE BERKELEY LAB, DIV LIFE SCI, BERKELEY, CA 94720; UNIV COPENHAGEN, PANUM INST, INST MED ANAT, STRUCT CELL BIOL UNIT, DK-2200 COPENHAGEN N, DENMARK; JACK BELL RES-CTR, VANCOUVER, BC V6H 3Z6, CANADA; DANISH CANC SOC, DIV CANC BIOL, DEPT TUMOR ENDOCRINOL, DK-2100 COPENHAGEN O, DENMARK
CYA USA; DENMARK; CANADA
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF

AMERICA, (8 DEC 1998) Vol. 95, No. 25, pp. 14821-14826.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC
20418.

ISSN: 0027-8424.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 28 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 1998:167874 SCISEARCH

GA The Genuine Article (R) Number: YY117

TI The G-protein G(13) but not G(12) mediates signaling from
lysophosphatidic

acid receptor via **epidermal growth factor**
receptor to Rho

AU Gohla A; Harhammer R; Schultz G (Reprint)

CS FREE UNIV BERLIN, INST PHARMAKOL, THIELALLEE 67-73, D-14195 BERLIN,
GERMANY (Reprint); FREE UNIV BERLIN, INST PHARMAKOL, D-14195 BERLIN,
GERMANY

CYA GERMANY

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (20 FEB 1998) Vol. 273, No. 8, pp.
4653-4659.

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE
PIKE, BETHESDA, MD 20814.

ISSN: 0021-9258.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 29 OF 73 MEDLINE

DUPLICATE 17

AN 1998187674 MEDLINE

DN 98187674

TI **Epidermal growth factor receptor**

activation in androgen-independent but not androgen-stimulated growth of
human prostatic carcinoma cells.

AU Sherwood E R; Van Dongen J L; Wood C G; Liao S; Kozlowski J M; Lee C

CS Department of Urology, Northwestern University Medical School, Chicago,
IL

60611, USA.

NC DK 39250 (NIDDK)

CA 58073 (NCI)

SO BRITISH JOURNAL OF CANCER, (1998 Mar) 77 (6) 855-61.

Journal code: AV4. ISSN: 0007-0920.

CY SCOTLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals...

EM 199806

L12 ANSWER 30 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1998174905 EMBASE

TI [Tyrosine kinase: Implications in tumorigenesis and new avenues for
cancer
treatment].

TYROSINE KINASE: IMPLICATIONS EN PATHOLOGIE Tumorale ET PERSPECTIVES
THERAPEUTIQUES.

AU Peyrade F.; Taillan B.; Lebrun C.; Baron V.; Dujardin P.
CS F. Peyrade, Svc. d'Hematologie-Medecine Interne, Hopital l'Archet I, BP
3079, 06202 Nice cedex 03, France
SO Revue de Medecine Interne, (1998) 19/5 (366-372).
Refs: 15
ISSN: 0248-8663 CODEN: RMEIDE
CY France
DT Journal; General Review
FS 006 Internal Medicine
016 Cancer
037 Drug Literature Index
LA French
SL English; French

L12 ANSWER 31 OF 73 MEDLINE DUPLICATE 18

AN 1998330492 MEDLINE

DN 98330492

TI **EGFR** blockade by tyrosine kinase inhibitor or monoclonal
antibody inhibits growth, directs terminal differentiation and
induces apoptosis in the human squamous cell carcinoma HN5.

AU Modjtahedi H; Affleck K; Stubberfield C; Dean C

CS The Institute of Cancer Research, McElwain Laboratories, Belmont, Sutton,
Surrey, UK.

SO INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Aug) 13 (2) 335-42.

Journal code: CX5. ISSN: 1019-6439.

CY Greece

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199810

L12 ANSWER 32 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 19

AN 1998:442844 BIOSIS

DN PREV199800442844

TI Anti-**EGFR** monoclonal **antibodies** which act as EGF,
TGFalpha, HB-EGF and BTC antagonists block the binding of epiregulin to
EGFR-expressing tumours.

AU Modjtahedi, Helmout (1); Komurasaki, Toshi; Toyoda, Hitoshi; Dean,
Christopher

CS (1) Inst. Cancer Res., McElwain Lab., Belmont, Sutton, Surrey SM2 5NG UK

SO International Journal of Cancer, (Jan. 19, 1998) Vol. 75, No. 2, pp.
310-316.

ISSN: 0020-7136.

DT Article

LA English

L12 ANSWER 33 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 1998:498091 SCISEARCH

GA The Genuine Article (R) Number: ZV933

TI Skin cancer chemopreventive effects of a flavonoid antioxidant silymarin
are mediated via impairment of receptor tyrosine kinase signaling and
perturbation in cell cycle progression

AU Ahmad N; Gali H; Javed S; Agarwal R (Reprint)

CS AMC CANC RES CTR, CTR CANC CAUSAT & PREVENT, 1600 PIERCE ST, DENVER, CO
80214 (Reprint); AMC CANC RES CTR, CTR CANC CAUSAT & PREVENT, DENVER, CO
80214; CASE WESTERN RESERVE UNIV, UNIV HOSP CLEVELAND, DEPT DERMATOL,

SKIN

DIS RES CTR, CLEVELAND, OH 44106; CASE WESTERN RESERVE UNIV, UNIV HOSP
CLEVELAND, IRELAND CANC CTR, CLEVELAND, OH 44106

CYA USA

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (18 JUN 1998) Vol.
247, No. 2, pp. 294-301.
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900,
SAN DIEGO, CA 92101-4495.
ISSN: 0006-291X.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 51
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 34 OF 73 MEDLINE

AN 1998069862 MEDLINE

DN 98069862

TI Cell scattering and migration induced by autocrine transforming growth
factor alpha in human glioma cells in vitro.

AU El-Obeid A; Bongcam-Rudloff E; Sorby M; Ostman A; Nister M; Westermarck B

CS Department of Pathology, Uppsala University, University Hospital,
Sweden.

SO CANCER RESEARCH, (1997 Dec 15) 57 (24) 5598-604.
Journal code: CNF. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199803

L12 ANSWER 35 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97036644 EMBASE

DN 1997036644

TI The enhanced tumorigenic activity of a mutant **epidermal
growth factor receptor** common in human cancers
is mediated by threshold levels of constitutive **tyrosine
phosphorylation** and unattenuated signaling.

AU Huang H.-J.S.; Nagane M.; Klingbeil C.K.; Hong Lin; Nishikawa R.; Ji X.-
D.; Huang C.-M.; Gill G.N.; Wiley H.S.; Cavenee W.K.

CS H.-J.S. Huang, Ludwig Institute for Cancer Research, 9500 Gilman Dr, San
Diego, CA 92093-0660, United States. hhuang@ucsd.edu

SO Journal of Biological Chemistry, (1997) 272/5 (2927-2935).
Refs: 72
ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry

LA English

SL English

L12 ANSWER 36 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 97:906724 SCISEARCH

GA The Genuine Article (R) Number: YJ803

TI Epiregulin binds to **epidermal growth factor
receptor** and ErbB-4 and induces **tyrosine
phosphorylation of epidermal growth**

factor receptor, ErbB-2, ErbB-3 and ErbB-4
AU Komurasaki T (Reprint); Toyoda H; Uchida D; Morimoto S
CS TAISHO PHARMACEUT CO LTD, MED RES LABS, MOL BIOL LAB, 1-403 YOSHINO CHO,
OHMIYASHI, SAITAMA 330, JAPAN (Reprint)
CYA JAPAN
SO ONCOGENE, (4 DEC 1997) Vol. 15, No. 23, pp. 2841-2848.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE, ENGLAND
RG21 6XS.
ISSN: 0950-9232.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 49
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 37 OF 73 MEDLINE DUPLICATE 20
AN 1998054129 MEDLINE
DN 98054129
TI Reduced ability of transforming growth factor-alpha to induce EGF
receptor
heterodimerization and downregulation suggests a mechanism of oncogenic
synergy with ErbB2.
AU Gulliford T J; Huang G C; Ouyang X; Epstein R J
CS Division of Medicine, Imperial College School of Medicine, Charing Cross
Hospital, London, UK.
NC R0169513
SO ONCOGENE, (1997 Oct) 15 (18) 2219-23..
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802

L12 ANSWER 38 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:193770 SCISEARCH
GA The Genuine Article (R) Number: WK897
TI Role of **epidermal growth factor**
receptor and STAT-3 activation in autonomous proliferation of
SUM-102PT human breast cancer cells
AU Sartor C I; Dziubinski M L; Yu C L; Jove R; Ethier S P (Reprint)
CS UNIV MICHIGAN, DEPT RADIAT ONCOL, DIV RADIAT & CANC BIOL, SCH MED, 1331 E.
ANN ST, ANN ARBOR, MI 48109 (Reprint); UNIV MICHIGAN, DEPT RADIAT ONCOL,
DIV RADIAT & CANC BIOL, SCH MED, ANN ARBOR, MI 48109; H LEE MOFFITT CANC
CTR, TAMPA, FL 33612
CYA USA
SO CANCER RESEARCH, (1 MAR 1997) Vol. 57, No. 5, pp. 978-987.
Publisher: AMER ASSOC CANCER RESEARCH, PUBLIC LEDGER BLDG, SUITE 816, 150
S. INDEPENDENCE MALL W., PHILADELPHIA, PA 19106.
ISSN: 0008-5472.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 39 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:502806 SCISEARCH

GA The Genuine Article (R) Number: XG558
 TI Receptor dimerization is not a factor in the signalling activity of a transforming variant **epidermal growth factor receptor** (EGFRVIII)
 AU Chu C T; Everiss K D; Wikstrand C J; Batra S K; Kung H J; Bigner D D (Reprint)
 CS DUKE UNIV, MED CTR, DEPT PATHOL, DURHAM, NC 27710 (Reprint); DUKE UNIV, MED CTR, DEPT PATHOL, DURHAM, NC 27710; DUKE UNIV, MED CTR, PREUSS LAB BRAIN TUMOR RES, DURHAM, NC 27710; CASE WESTERN RESERVE UNIV, DEPT MOL BIOL & MICROBIOL, CLEVELAND, OH 44106; UNIV NEBRASKA, MED CTR, DEPT BIOCHEM & MOL BIOL, OMAHA, NE 68198
 CYA USA
 SO BIOCHEMICAL JOURNAL, (15 JUN 1997) Vol. 324, Part 3, pp. 855-861. Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ. ISSN: 0264-6021.
 DT Article; Journal
 FS LIFE
 LA English
 REC Reference Count: 44
 ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 40 OF 73 MEDLINE DUPLICATE 21
 AN 1998012851 MEDLINE
 DN 98012851
 TI Modulation of the Kv1.3 potassium channel by receptor tyrosine kinases.
 AU Bowlby M R; Fadool D A; Holmes T C; Levitan I B
 CS Department of Biochemistry and Volen Center for Complex Systems, Brandeis University, Waltham, Massachusetts 02254, USA.
 SO JOURNAL OF GENERAL PHYSIOLOGY, (1997 Nov) 110 (5) 601-10. Journal code: I8N. ISSN: 0022-1295.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199802

L12 ANSWER 41 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
 AN 97:870328 SCISEARCH
 GA The Genuine Article (R) Number: YG489
 TI Immunohistochemical assessment of proliferation markers and altered gene expression in archival specimens of ovarian epithelial tumors
 AU Khalifa M A (Reprint); Lacher D A; Lage J M; Mannel R S; Walker J L; Angros L H; Min K W
 CS MEM UNIV NEWFOUNDLAND, GEN HOSP, DEPT PATHOL, ST JOHNS, NF A1B.3V6, CANADA
 (Reprint); MEM UNIV NEWFOUNDLAND, DEPT PATHOL, ST JOHNS, NF, CANADA
 CYA CANADA
 SO CANCER DETECTION AND PREVENTION, (NOV-DEC 1997) Vol. 21, No. 6, pp. 532-539. Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148. ISSN: 0361-090X.
 DT Article; Journal
 FS CLIN
 LA English
 REC Reference Count: 45
 ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 42 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 22

AN 1997:261498 BIOSIS
 DN PREV199799568101
 TI Monoclonal **antibodies** directed against the EGF receptor show differential bindings of amphiregulin and EGF to the EGF receptor.
 AU Modjtahedi, Helmout (1); Cohen, Bruce D.; Dean, Christopher
 CS (1) Inst. Cancer Res., McElwain Lab., 15 Cotswold Road, Belmont, Sutton, Surrey SM2 5NG UK
 SO International Journal of Oncology, (1997) Vol. 10, No. 2, pp. 339-347. ISSN: 1019-6439.
 DT Article
 LA English

L12 ANSWER 43 OF 73 MEDLINE DUPLICATE 23
 AN 97346252 MEDLINE
 DN 97346252
 TI Protein kinase C inhibits **epidermal growth factor receptor** phosphorylation in enterocytes.
 AU Summers S T; Bass B L
 CS Department of Surgery, Veteran's Administration Medical Center, Baltimore, Maryland 21201, USA.
 SO JOURNAL OF SURGICAL RESEARCH, (1997 Apr) 69 (1) 208-11. Journal code: K7B. ISSN: 0022-4804.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199709

L12 ANSWER 44 OF 73 MEDLINE DUPLICATE 24
 AN 97126968 MEDLINE
 DN 97126968
 TI Inhibition of **epidermal growth factor receptor**-associated tyrosine kinase blocks glioblastoma invasion of the brain.
 AU Penar P L; Khoshyomn S; Bhushan A; Tritton T R
 CS Division of Neurosurgery, University of Vermont College of Medicine, Burlington, USA.
 SO NEUROSURGERY, (1997 Jan) 40 (1) 141-51. Journal code: NZL. ISSN: 0148-396X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199705

L12 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2001 ACS
 AN 1996:71580 CAPLUS
 DN 124:114575
 TI Isolated polypeptide erbB-3, related to the **epidermal growth factor receptor** and antibody thereto
 IN Kraus, Matthias H.; Aaronson, Stuart A.
 PA United States Dept. of Health and Human Services, USA
 SO U.S., 41 pp. Cont.-in-part of U.S. 5,183,884. CODEN: USXXAM
 DT Patent
 LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5480968	A	19960102	US 1992-978895	19921110
	US 444406	A0	19910315	US 1989-444406	19891201
	US 5183884	A	19930202		
	US 5820859	A	19981013	US 1995-473119	19950607
	US 5916755	A	19990629	US 1995-475352	19950607
PRAI	US 1989-444406		19891201		
	US 1992-978895		19921110		

L12 ANSWER 46 OF 73 MEDLINE DUPLICATE 25
 AN 96215237 MEDLINE
 DN 96215237
 TI Involvement of ErbB2 in the signaling pathway leading to cell cycle progression from a truncated **epidermal growth factor receptor** lacking the C-terminal autophosphorylation sites.
 AU Sasaoka T; Langlois W J; Bai F; Rose D W; Leitner J W; Decker S J; Saltiel
 A; Gill G N; Kobayashi M; Draznin B; Olefsky J M
 CS First Department of Medicine, Toyama Medical and Pharmaceutical University, Toyama, 930-01, Japan.
 NC DK33651 (NIDDK)
 DK13149 (NIDDK)
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Apr 5) 271 (14) 8338-44.
 Journal code: HIV. ISSN: 0021-9258.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199608

L12 ANSWER 47 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
 AN 96:675245 SCISEARCH
 GA The Genuine Article (R) Number: VG135
 TI TARGETED INHIBITION OF TUMOR-CELL GROWTH BY A BISPECIFIC SINGLE-CHAIN TOXIN CONTAINING AN***ANTIBODY** DOMAIN AND TGF-ALPHA
 AU SCHMIDT M; WELS W (Reprint)
 CS INST EXPT CANC RES, TUMOR BIOL CTR, POB 1120, D-79011 FREIBURG, GERMANY (Reprint); INST EXPT CANC RES, TUMOR BIOL CTR, D-79011 FREIBURG, GERMANY; UNIV FREIBURG, DEPT BIOL, FREIBURG, GERMANY
 CYA GERMANY
 SO BRITISH JOURNAL OF CANCER, (SEP 1996) Vol. 74, No. 6, pp. 853-862.
 ISSN: 0007-0920.
 DT Article; Journal
 FS LIFE; CLIN
 LA ENGLISH
 REC Reference Count: 28
 ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 48 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)
 AN 96:99708 SCISEARCH
 GA The Genuine Article (R) Number: TR538
 TI BETACELLULIN ACTIVATES THE **EPIDERMAL GROWTH-FACTOR RECEPTOR** AND ERBB-4, AND INDUCES CELLULAR-RESPONSE PATTERNS DISTINCT FROM THOSE STIMULATED BY EPIDERMAL GROWTH-FACTOR OR NEUREGULIN-BETA

AU RIESE D J; BERMINGHAM Y; VANRAAIJ T M; BUCKLEY S; PLOWMAN G D; STERN D F
(Reprint)
CS YALE UNIV, SCH MED, DEPT PATHOL, 333 CEDAR ST, NEW HAVEN, CT, 06520
(Reprint); YALE UNIV, SCH MED, DEPT PATHOL, NEW HAVEN, CT, 06520; BRISTOL
MYERS SQUIBB PHARMACEUT RES INST, SEATTLE, WA, 98121; SUGEN INC, REDWOOD
CITY, CA, 94063
CYA USA
SO ONCOGENE, (18 JAN 1996) Vol. 12, No. 2, pp. 345-353.
ISSN: 0950-9232.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 54
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 49 OF 73 MEDLINE DUPLICATE 26

AN 96313262 MEDLINE
DN 96313262
TI Intracellular expression of a single-chain **antibody** directed to
the **EGFR** leads to growth inhibition of tumor cells.
AU Jannot C B; Beerli R R; Mason S; Gullick W J; Hynes N E
CS Friedrich Miescher Institute, Basel, Switzerland.
SO ONCOGENE, (1996 Jul 18) 13 (2) 275-82.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199611

L12 ANSWER 50 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 27

AN 1996:239871 BIOSIS
DN PREV199698788000
TI UV activates growth factor receptors via reactive oxygen intermediates.
AU Huang, Ruo-Pan; Wu, Jie-Xin; Fan, Yan; Adamson, Eileen D. (1)
CS (1) La Jolla Cancer Res. Foundation, 10901 N. Torrey Pines Rd., La Jolla,
CA 92037 USA
SO Journal of Cell Biology, (1996) Vol. 133, No. 1, pp. 211-220.
ISSN: 0021-9525.
DT Article
LA English

L12 ANSWER 51 OF 73 MEDLINE DUPLICATE 28

AN 95197672 MEDLINE
DN 95197672
TI Association of **epidermal growth factor**
receptors with coated pit adaptins via a **tyrosine**
phosphorylation-regulated mechanism.
AU Nesterov A; Kurten R C; Gill G N
CS Department of Medicine, University of California at San Diego, La Jolla
92093.
NC PO1 CA58689 (NCI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Mar 17) 270 (11) 6320-7.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals

EM 199506

L12 ANSWER 52 OF 73 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 29
AN 1995:495418 BIOSIS
DN PREV199598518968
TI **Antibody**-induced inhibition of growth of **EGFR**
overexpressing occurs in the absence of receptor down-regulation.
AU Modjtahedi, Helmout; Dean, Christopher
CS Inst. Cancer Res., Section Immunol., Sutton, Surrey SM2 5NG UK
SO International Journal of Oncology, (1995) Vol. 7, No. 4, pp. 783-788.
ISSN: 1019-6439.
DT Article
LA English

L12 ANSWER 53 OF 73 MEDLINE
AN 95032035 MEDLINE
DN 95032035
TI Nuclear localization of p185neu tyrosine kinase and its association with
transcriptional transactivation.
AU Xie Y; Hung M C
CS Department of Tumor Biology, University of Texas M. D. Anderson Cancer
Center, Houston 77030.
NC CA58880 (NCI)
CA60856 (NCI)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Sep 30) 203
(3)
1589-98.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501

L12 ANSWER 54 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1994:401881 CAPLUS
DN 121:1881
TI Increased levels and constitutive **tyrosine**
phosphorylation of the **epidermal growth**
factor receptor contribute to autonomous growth of human
papilloma virus type 16 immortalized human keratinocytes
AU Zyzak, Li Li; MacDonald, Lisa M.; Batova, Ayse; Forand, Ronald; Creek,
Kim
E.; Pirisi, Lucia
CS Sch. Med., Univ. South Carolina, Columbia, SC, 29208, USA
SO Cell Growth Differ. (1994), 5(5), 637-47
CODEN: CGDIE7; ISSN: 1044-9523
DT Journal
LA English

L12 ANSWER 55 OF 73 MEDLINE DUPLICATE 30
AN 94325221 MEDLINE
DN 94325221
TI Increased levels and constitutive **tyrosine**
phosphorylation of the **epidermal growth**
factor receptor contribute to autonomous growth of human
papillomavirus type 16 immortalized human keratinocytes.
AU Zyzak L L; MacDonald L M; Batova A; Forand R; Creek K E; Pirisi L

CS Department of Pediatrics, University of South Carolina School of
Medicine,
Columbia.

NC R29CA48990 (NCI)

SO CELL GROWTH AND DIFFERENTIATION, (1994 May) 5 (5) 537-47.
Journal code: AYH. ISSN: 1044-9523.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199411

L12 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2001 ACS

AN 1994:209532 CAPLUS

DN 120:209532

TI Peptides that bind ligands of the **epidermal growth
factor receptor** and erbB-2-receptor

IN Lupu, Ruth; Lippman, Marc

PA Georgetown University, USA

SO PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9322339	A1	19931111	WO 1993-US4055	19930429
	W: AU, CA, JP, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9342244	A1	19931129	AU 1993-42244	19930429
	AU 676476	B2	19970313		
	EP 641358	A1	19950308	EP 1993-910919	19930429
	EP 641358	B1	20000315		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 08502241	T2	19960312	JP 1993-519523	19930429
	AT 190626	E	20000415	AT 1993-910919	19930429
	US 5874528	A	19990223	US 1994-117187	19941027
PRAI	US 1992-875788		19920429		
	US 1992-917988		19920724		
	US 1990-528438		19900525		
	US 1991-640497		19910114		
	US 1992-872114		19920422		
	WO 1993-US4055		19930429		

L12 ANSWER 57 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 31

AN 93260696 EMBASE

DN 1993260696

TI eps15, A novel tyrosine kinase substrate, exhibits transforming
activity.

AU Fazioli F.; Minichiello L.; Matoskova B.; Wong W.T.; Di Fiore P.P.

CS Lab. of Cellular/Molecular Biology, National Cancer Institute, Bethesda,
MD

20892, United States

SO Molecular and Cellular Biology, (1993) 13/9 (5814-5828).

ISSN: 0270-7306 CODEN: MCEBD4

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry
LA English
SL English

L12 ANSWER 58 OF 73 MEDLINE DUPLICATE 32
AN 93155115 MEDLINE
DN 93155115
TI Amphiregulin induces **tyrosine phosphorylation** of the
epidermal growth factor receptor and
p185erbB2. Evidence that amphiregulin acts exclusively through the
epidermal growth factor receptor at
the surface of human epithelial cells.
AU Johnson G R; Kannan B; Shoyab M; Stromberg K
CS Laboratory of Cell Biology, Food and Drug Administration, Bethesda,
Maryland 20892.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Feb 5) 268 (4) 2924-31.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199305

L12 ANSWER 59 OF 73 MEDLINE
AN 93219392 MEDLINE
DN 93219392
TI Demonstration of ligand-dependent signaling by the erbB-3 tyrosine kinase
and its constitutive activation in human breast tumor cells.
AU Kraus M H; Fedi P; Starks V; Muraro R; Aaronson S A
CS Laboratory of Cellular and Molecular Biology, National Cancer Institute,
Bethesda, MD 20892.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (1993 Apr 1) 90 (7) 2900-4.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199307

L12 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2001 ACS
AN 1994:24253 CAPLUS
DN 120:24253
TI Down-modulation of **epidermal growth factor**
receptor accompanies TNF-induced differentiation of the DiFi human
adenocarcinoma cell line toward a goblet-like phenotype
AU Novotny-Smith, C. L.; Zorbas, M. A.; McIsaac, A. M.; Irimura, T.; Boman,
Bruce M.; Yeoman, L. C.; Gallick, G. E.
CS M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SO J. Cell. Physiol. (1993), 157(2), 253-62
CODEN: JCLLAX; ISSN: 0021-9541
DT Journal
LA English

L12 ANSWER 61 OF 73 MEDLINE DUPLICATE 33
AN 93179513 MEDLINE
DN 93179513
TI Anti-**epidermal growth factor**

receptor monoclonal antibodies affecting signal transduction.

AU Reins H A; Steinhilber G; Freiberg B; Anderer F A
CS Friedrich-Miescher-Laboratorium der Max-Planck-Gesellschaft, Tuebingen, Federal Republic of Germany.
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1993 Feb) 51 (2) 236-48.
Journal code: HNF. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306

L12 ANSWER 62 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 92:445454 SCISEARCH

GA The Genuine Article (R) Number: JF088

TI **TYROSINE PHOSPHORYLATION** OF MITOGEN-ACTIVATED PROTEIN-KINASE IN CELLS WITH TYROSINE KINASE-NEGATIVE **EPIDERMAL GROWTH-FACTOR RECEPTORS**

AU CAMPOSGONZALEZ R (Reprint); GLENNEY J R

CS UNIV KENTUCKY, LUCILLE P MARKEY CANC CTR, COMBS BLDG, RM 227, 800 ROSE ST,

LEXINGTON, KY, 40536 (Reprint); UNIV KENTUCKY, DEPT BIOCHEM, LEXINGTON, KY, 40536

CYA USA

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (25 JUL 1992) Vol. 267, No. 21, pp. 14535-14538.

ISSN: 0021-9258.

DT Note; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 63 OF 73 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 92287258 EMBASE

DN 1992287258

TI Epidermal growth factor stimulates **tyrosine phosphorylation** in the neonatal mouse: Association of a M(r) 55,000 substrate with the receptor.

AU Donaldson R.W.; Cohen S.

CS Department of Biochemistry, Vanderbilt Univ. School of Medicine, Nashville,

TN 37232, United States

SO Proceedings of the National Academy of Sciences of the United States of America, (1992) 89/18 (8477-8481).

ISSN: 0027-8424 CODEN: PNASA6

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

SL English

L12 ANSWER 64 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 34

AN 92:167053 SCISEARCH

GA The Genuine Article (R) Number: HH747

TI IDENTIFICATION AND BIOCHEMICAL-CHARACTERIZATION OF NOVEL PUTATIVE SUBSTRATES FOR THE **EPIDERMAL GROWTH-FACTOR**

RECEPTOR KINASE

AU FAZIOLI F; BOTTARO D P; MINICHELLO L; AURICCHIO A; WONG W T; SEGATTO O;
DIFIORE P P (Reprint)

CS NCI, CELLULAR & MOLEC BIOL LAB, BLDG 37, RM 1D23, BETHESDA, MD, 20892

CYA USA

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (15 MAR 1992) Vol. 267, No. 8, pp.
5155-5161.
ISSN: 0021-9258.

DT Article; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 46
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 65 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 92:120807 SCISEARCH

GA The Genuine Article (R) Number: HE606

TI P185C-NEU AND **EPIDERMAL GROWTH-FACTOR**
RECEPTOR ASSOCIATE INTO A STRUCTURE COMPOSED OF ACTIVATED KINASES

AU QIAN X L; DECKER S J; GREENE M I (Reprint)

CS UNIV PENN, SCH MED, DEPT PATHOL & LAB MED, PHILADELPHIA, PA, 19104; UNIV
PENN, SCH MED, DEPT BIOL, PHILADELPHIA, PA, 19104; PARKE DAVIS & CO, DIV
PHARMACEUT RES, ANN ARBOR, MI, 48106

CYA USA

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (15 FEB 1992) Vol. 89, No. 4, pp. 1330-1334.
ISSN: 0027-8424.

DT Article; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 66 OF 73 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 92:318395 SCISEARCH

GA The Genuine Article (R) Number: HU832

TI ANTIGEN RESPONSIVE **ANTIBODY-RECEPTOR KINASE CHIMERA**

AU UEDA H; KIKUCHI M; YAGI S; NISHIMURA H (Reprint)

CS UNIV TOKYO, FAC ENGN, DEPT CHEM ENGN, 7-3-1 HONGO, BUNKYO KU, TOKYO 113,
JAPAN

CYA JAPAN

SO BIO-TECHNOLOGY, (APR 1992) Vol. 10, No. 4, pp. 430-433.
ISSN: 0733-222X.

DT Article; Journal

FS LIFE; AGRI

LA ENGLISH

REC Reference Count: 43
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L12 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2001 ACS

AN 1992:52332 CAPLUS

DN 116:52332

TI Association of the tyrosine phosphorylated **epidermal**
growth factor receptor with a 55-kD tyrosine
phosphorylated protein at the cell surface and in endosomes

AU Wada, Ikuo; Lai, Wei H.; Posner, Barry I.; Bergeron, John J. M.

CS Dep. Anat., McGill Univ., Montreal, PQ, H3A 2B2, Can.

SO J. Cell Biol. (1992), 116(2), 321-30

CODEN: JCLBA3; ISSN: 0021-9525

DT Journal
LA English

L12 ANSWER 68 OF 73 MEDLINE

DUPLICATE 35

AN 91271361 MEDLINE

DN 91271361

TI Phosphorylation of protein 4.1 on tyrosine-418 modulates its function in vitro.

AU Subrahmanyam G; Bertics P J; Anderson R A

CS Department of Pharmacology, University of Wisconsin Medical School, Madison 53706.

NC GM38906 (NIGMS)

CA47881 (NCI)

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 Jun 15) 88 (12) 5222-6.

Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199109

L12 ANSWER 69 OF 73 MEDLINE

AN 92109790 MEDLINE

DN 92109790

TI Active c-erbB-2 induces short-term growth of FDC-P2 cells after IL-3 depletion.

AU Wongsasant B; Matsuda S; Yamamoto T

CS Department of Oncology, University of Tokyo, Japan.

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1991 Dec 31) 181 (3)

981-8.

Journal code: 9Y8. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199204

L12 ANSWER 70 OF 73 MEDLINE

AN 92110038 MEDLINE

DN 92110038

TI Immunodetection of the ligand-activated receptor for epidermal growth factor.

AU Campos-Gonzalez R; Glenney J R Jr

CS Department of Biochemistry, University of Kentucky, Lexington 40536-0093.

NC GM-32866 (NIGMS)

SO GROWTH FACTORS, (1991) 4 (4) 305-16.

Journal code: AOI. ISSN: 0897-7194.

CY Switzerland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199204

L12 ANSWER 71 OF 73 MEDLINE

DUPLICATE 36

AN 91019412 MEDLINE
 DN 91019412
 TI Direct interaction of a ligand for the erbB2 oncogene product with the
 EGF receptor and p185erbB2.
 AU Lupu R; Colomer R; Zugmaier G; Sarup J; Shepard M; Slamon D; Lippman M E
 CS Vincent T. Lombardi Cancer Research Center, Georgetown University Medical
 Center, Washington, DC 20007.
 SO SCIENCE, (1990 Sep 28) 249 (4976) 1552-5.
 Journal code: UJ7. ISSN: 0036-8075.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Cancer Journals; Priority Journals
 EM 199101

L12 ANSWER 72 OF 73 MEDLINE DUPLICATE 37

AN 90338148 MEDLINE
 DN 90338148
 TI Cellular distribution and biological activity of **epidermal growth factor receptors** in A431 cells are influenced by cell-cell contact.
 AU Lichtner R B; Schirmacher V
 CS Department of Immunology and Genetics, German Cancer Research Center, Heidelberg, Federal Republic of Germany.
 SO JOURNAL OF CELLULAR PHYSIOLOGY, (1990 Aug) 144 (2) 303-12.
 Journal code: HNB. ISSN: 0021-9541.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199011

L12 ANSWER 73 OF 73 MEDLINE DUPLICATE 38

AN 90147745 MEDLINE
 DN 90147745
 TI Expression of **epidermal growth factor receptor** sequences as E. coli fusion proteins: applications in the study of tyrosine kinase function.
 AU Koland J G; O'Brien K M; Cerione R A
 CS Department of Pharmacology, NYS College of Veterinary Medicine, Cornell University, Ithaca 14853.
 NC GM40654 (NIGMS)
 SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1990 Jan 15) 166 (1) 90-100.
 Journal code: 9Y8. ISSN: 0006-291X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199005

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---Logging off of STN---

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COST IN U.S. DOLLARS

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

CA SUBSCRIBER PRICE

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Association of the Tyrosine Phosphorylated Epidermal Growth Factor Receptor with a 55-kD Tyrosine Phosphorylated Protein at the Cell Surface and in Endosomes

Iku Wada, Wei H. Lai, Barry I. Posner,* and John J. M. Bergeron

Departments of Anatomy and Medicine,* McGill University, Montreal, Quebec, Canada H3A 2B2

Abstract. After the intraportal injection of EGF, the EGF receptor (EGFR) is rapidly internalized into hepatic endosomes where it remains largely receptor bound (Lai et al., 1989. *J. Cell Biol.* 109:2751-2760). In the present study, we evaluated the phosphotyrosine content of EGFRs at the cell surface and in endosomes in order to assess the consequences of internalization. Quantitative estimates of specific radioactivity of the EGFR in these two compartments revealed that tyrosine phosphorylation of the EGFR was observed at the cell surface within 30 s of ligand administration. However, the EGFR was also highly phosphorylated in endosomes reaching levels of tyrosine phosphorylation significantly higher than those of the cell surface receptor at 5 and 15 min after EGF injection. A 55-kD

tyrosine phosphorylated polypeptide (pyp55) was observed in association with the EGFR at the cell surface within 30 s of EGF injection. The protein was also found in association with the EGFR in endosomes as evidenced by coprecipitation studies using a mAb to the EGFR as well as by coelution with the EGFR in gel permeation chromatography. Limited proteolysis of isolated endosomes indicated that the tyrosine phosphorylated domains of the EGFR and associated pyp55 were cytosolically oriented while internalized EGFR was intraluminal. The identification of pyp55 in association with EGFR in both hepatic plasma membranes and endosomes may be relevant to EGFR function and/or trafficking of the EGFR.

WE and others have used subcellular fractionation and associated approaches in an attempt to delineate the components of rat liver involved in insulin, prolactin, and EGF receptor (EGFR) internalization in vivo (Bergeron et al., 1985; Dunn and Hubbard, 1986; Khan et al., 1986, 1989; Lai et al., 1989a,b). Past studies have revealed that after internalization into endosomes (5-15 min) the ligand, EGF, remained largely associated with the periphery of endosomes. This was revealed by EM radioautography of the distribution of silver grains from [¹²⁵I]EGF within endosomes in situ of the placental syncytiotrophoblast (Lai et al., 1986) and for the distribution of [¹²⁵I]EGF within isolated rat liver endosomes (Lai et al., 1989b). Direct visualization of internalized EGF by protein-A gold EM immunolabeling of endosomes in A431 cells has been demonstrated by Carpentier et al. (1987) and biochemical studies that evaluated the degree of ligand receptor association after polyethylene glycol precipitation of the complexes from solubilized endosomes revealed that the majority of internalized EGF within such components of liver parenchymal cells was receptor bound (Lai et al., 1989b). These studies as well as the observations that demonstrated enhanced autophosphorylation activity of the EGFR in isolated rat liver endosomes (Kay et al., 1986; Lai et al., 1989b) predicted that the

phosphotyrosine content of the EGFR subsequent to internalization must remain elevated at least during transit of the receptor through the endosomal compartment(s). We have attempted to test this prediction by quantitation of the in vivo state of tyrosine phosphorylation of the receptor at the cell surface and after internalization into endosomes. Larkin et al. (1986) demonstrated the feasibility of labeling hepatic receptors such as the polymeric IgA receptor after whole animal injection of ³²Pi. We have consequently followed this approach to label the EGFR in vivo, and in conjunction with antibodies specific to phosphotyrosine, have observed that the EGFR is indeed highly tyrosine phosphorylated after internalization into endosomes after initial phosphorylation at the cell surface. Furthermore, we have observed a novel tyrosine phosphorylated protein of 55 kD (pyp55) in association with the EGFR both at the cell surface and after receptor internalization into endosomes. The orientation of the EGFR and pyp55 in isolated endosomes is such that their tyrosine phosphorylated domains are cytosolically oriented.

Materials and Methods

Materials

EGF was purchased from Collaborative Research (Waltham, MA) and insulin was a gift from the Connaught Laboratories (Toronto, Ontario). [³²P]-ATP (3,000 Ci/mmol), [³²P]orthophosphate (900 mCi/mmol), and Na[¹²⁵I]

1. **Abbreviations used in this paper:** EGFR, EGF receptor; GE, Golgi endosomal; PM, plasma membrane.

were purchased from DuPont Canada (Mississauga, Ontario). Thin layer plates (E. Merck; 0.1 mm cellulose, 20 × 20 cm) were obtained from BDH (Montreal, Quebec). All other chemicals were from Sigma Chemical Co. (St. Louis, MO), Anachemia Canada Inc. (Lachine, Quebec), and Boehringer Mannheim (Montreal, Quebec). Sprague-Dawley rats were obtained from Charles River Ltd. (St. Constant, Quebec). For all experiments, rats were injected via the hepatic portal vein and sacrificed at various times after the injection of saturating doses (Lai et al., 1989a) of EGF (10 µg/100 g bw).

Antibodies

The hybridoma secreting anti-EGFR mAb was a gift from Dr. C. E. Chandler and was subcloned (IgG-151, BH-6) by Drs. W. A. Dunn and A. L. Hubbard (The Johns Hopkins University, Baltimore, MD). The antibodies were isolated from hybridomas as described by Lai et al. (1989b). Phosphotyrosine was conjugated to keyhole limpet hemocyanin by using 1-ethyl-3-(3-dimethyl amino)-1-naphthalene-sulfonic acid and was used to raise antibodies against phosphotyrosine in rabbits. Antibodies were obtained by phosphotyrosine conjugated to Affigel 15 (Bio Rad, Mississauga, Ontario) column chromatography. The specificity of the antibodies was evaluated by immunoprecipitation and immunoblotting of the tyrosine phosphorylated EGFR. Thus, both immunoprecipitation and Western blotting were inhibited by phosphotyrosine but not phosphoserine or phosphothreonine (not shown). Site-specific antibodies against peptide P1 (residues 1,164–1,176 KGSTRENAEYLRLV) and against peptide P3 (DDTFLPVEYINQS, residues 1,059–1,072) of the EGFR (Downward et al., 1984) were synthesized by Dr. N. Ling (The Salk Institute, San Diego, CA). The peptides were coupled to keyhole limpet hemocyanin and polyclonal antibodies were raised after injection into rabbits (Lai et al., 1989a).

In Vivo Labeling of Animals, Preparation of Plasma Membrane and Endosome Fractions, Determination of Receptor Content

Male Sprague-Dawley rats (120–130 g) received 5 mCi of [³²P]orthophosphate via the portal vein. EGF also was injected via the portal vein. The livers were removed at 1 h after the injection of [³²P] orthophosphate and homogenized immediately in ice-cold homogenization buffer (0.25 M sucrose, 1 mM MgCl₂, 5 mM iodoacetamide, 4 mM NaF, 100 µM Na₂VO₄, 10 mM β-glycerophosphate, 5 mM p-nitrophenylphosphate, 5 mM Na₂MoO₄, 0.5 mM ATP, 2 mM benzamide, 500 KIU Aprotinin per ml, 0.5 mM PMSF, 20 mM Tris-HCl, pH 7.5) with the Dounce homogenizer (type B) to give a 15% (wt/vol) homogenate. The plasma membrane (PM) fraction was isolated from the homogenate basically as described by Kay et al. (1986) except for the addition of 0.5 mM ATP, 10 mM β-glycerophosphate, 5 mM p-nitrophenylphosphate (final concentrations) to the homogenate and all centrifugation buffers. The PM fraction was subsequently purified from the combined 280-g and 1,500-g pellets as described by Kay et al. (1986) and Lai et al. (1989a). The resultant supernatant was used to purify the endosome (GE) fractions. The supernatant was adjusted to 1.1 M sucrose by adding 2.3 M sucrose in homogenization buffer (vide supra). A discontinuous gradient of 0.4 and 0.95 M sucrose containing the same buffer constituents as above was overlaid above the load zone (1:1 vol). Subsequent centrifugation (85,000 g_{av} for 150 min, Beckman SW28 rotor without the brake) yielded a GE fraction at the interface of the 0.4 and 0.95 M sucrose layers. The fraction was identical to that described by Kay et al. (1986), Lai et al. (1989a,b) and Doherty et al. (1990) as evaluated by EM, SDS-PAGE, ligand binding ([¹²⁵I]EGF), and the enzyme activities of 5' nucleotidase and galactosyl transferase (data not shown).

At 0, 0.5, 5, and 15 min after the portal vein injection of EGF (10 µg/100 g bw), PM and GE fractions were prepared and EGFR content was evaluated. However, the high concentration of internalized EGF in GE fractions prevented the determination of EGFR content from inhibition dose response binding data (Lai et al., 1989a). Consequently immunoblotting, using site-specific antibody directed against peptide P1 of the EGFR (vide supra, followed by densitometry as described by Lai et al. (1989a) [see Fig. 3 of this reference]) was used to determine a linear relationship between densitometry and receptor content over a range of 5–100 µg of subcellular fraction protein. The densitometric units derived from immunoblotting were normalized for the EGFR content of PM and GE fractions isolated from the livers of control (noninjected) rats as determined from [¹²⁵I]EGF inhibition dose response binding data.

Immunoprecipitation

PM or GE fractions were pelleted by centrifugation at 10,000 g for 30 min

(PM) or 100,000 g for 45 min (GE) after a fourfold dilution with the homogenization buffer. To precipitate the EGFR, membranes were solubilized with 5% Triton X-100, 2.5% sodium deoxycholate, 10% glycerol, 0.15 M NaCl, 5 mM iodoacetamide, 5 mM p-nitrophenylphosphate, 2 mM Na₂VO₄, 20 mM NaF, 10 mM β-glycerophosphate, 50 mM sodium phosphate buffer, pH 7.5, at 4°C for 30 min and diluted 10-fold with 0.1% BSA, 0.15 M NaCl, 5 mM p-nitrophenylphosphate, 100 mM sodium phosphate buffer, pH 6, then centrifuged at 50,000 g for 30 min. mAb against the EGFR (100 µg protein, IgG) was added to the supernatant (from 1 mg protein of PM or GE) and incubated for 15 min at 0°C followed by another incubation with Pansorbin for 1 h at 4°C. The immune complex was washed five times (5 min, 10,000 g) with 0.1% BSA, 0.1% Triton X-100, 0.15 M NaCl, 2 mM Na₂VO₄, 10 mM β-glycerophosphate, 100 mM sodium phosphate buffer, pH 7.5. The immune complex was resuspended in 1.5% SDS, 5% glycerol, 50 mM Tris-HCl, pH 6.8, 5% β-mercaptoethanol, and incubated for 15 min at 65°C. SDS-PAGE was carried out with a gradient gel of 5–15% acrylamide. Resolved phosphoproteins on the gel were visualized by radioautography using Kodak X-OMAT X-ray films with enhancing screens. Intensity of the bands was quantified by densitometry with a Zeineh soft laser scanning densitometer interfaced with an IBM PC using a GS350 Data System (Hoffler Scientific Instruments).

Gel Permeation Chromatography of Endosomal Proteins

The GE fraction was solubilized as described for immunoprecipitation (vide supra). The solubilized endosomes were filtered through a 0.22-µm filter and immediately applied onto a TSK 3000 SW column equilibrated with 0.15 M NaCl, 0.2% Tween 20, 10% glycerol, 0.1 mM sodium vanadate, 10 mM Tris-HCl, pH 7.5. The eluant (0.2 ml/min/tube) was fractionated by reversed phase HPLC and 1 ml of 80% ethanol/20% n-hexanes was added immediately into each fraction.

Peptide Mapping

Peptide mapping of [¹²⁵I]EGFR and [¹²⁵I]pyp55 was effected as follows: GE fractions isolated at 15 min after injection of EGF were solubilized with 1% Triton X-100, 0.5% deoxycholate, 10 mM Tris-HCl, pH 7.5, 10% glycerol for 15 min on ice and were incubated with ~10 U of alkaline phosphatase (purified from Bovine intestinal mucosa; Sigma Chemical Co., Type VII-N) for 10 min at room temperature. The sample was iodinated with 1 mCi of Na[¹²⁵I] by using Iodo Beads (Pierce). Free iodine was removed by Sephadex G-25 (10 × 50 mm) column chromatography equilibrated with 0.1% BSA, 0.1% Triton X-100, 10% glycerol, 0.15 M NaCl, 10 mM Tris-HCl, pH 7.5. The void fraction was centrifuged at 100,000 g for 30 min after preincubation with Pansorbin for 15 min at room temperature (in order to remove nonspecific binding to Pansorbin). The supernatant was then incubated with EGFR antibody for 15 min at room temperature followed by another incubation with Pansorbin for 10 min at room temperature. The immune complex was recovered by centrifugation (10,000 g for 5 min) and washed as described above. The immune complex was treated under nonreducing conditions in order to minimize contamination with IgG heavy chain with 1.5% SDS, 5% glycerol, 50 mM Tris-HCl, pH 6.8, at 65°C for 10 min and resolved by SDS-PAGE. The bands corresponding to the EGFR and pyp55 were excised and tryptic peptides were obtained as follows: gel pieces were washed with 85% acetone, 5% triethylamine, 5% acetic acid, 5% water, followed by 50 mM N-ethylmorpholine, then homogenized in 1 ml of 50 mM N-ethylmorpholine as described by Tornqvist et al. (1987). The gel suspensions were incubated with 50 µg of TPCK trypsin for 3 h at 37°C with rotation followed by incubation with another 50 µg/ml of TPCK trypsin for 10–12 h at 37°C as described by Tornqvist et al. (1987). [¹²⁵I] peptides were then resolved on cellulose plates at 500 V for 30 min in 30% formic acid for the 1st dimension, and the second dimension was chromatographed in n-butanol, acetic acid, pyridine, H₂O (6:12:40:48) as described in Fig. 4. The plates were exposed to X-ray film for 1 wk (EGFR) or 30 d (pyp55) after staining with ninhydrin.

Limited Protease Digestion of the EGFR in Endosomes

GE fractions were isolated 15 min after the injection of 10 µg/100 g bw of EGF as described (Lai et al., 1989a,b) in the presence of the phosphatase inhibitors, 2 mM NaF, 100 µM Na₂VO₄, and 5 mM p-nitrophenylphosphate. Fractions (25 µg membrane protein) were incubated with increasing concentrations of trypsin at 0°C for 30 min in the presence or absence of Triton X-100 following which aprotinin at 2.5 times the respective concentration of trypsin was added.

Results

Subcellular fractionation was employed to separate hepatic PM from endosome fractions of liver homogenates prepared at various times after the intraportal injection of saturating doses of EGF (10 μ g/100 g bw; Lai et al., 1989a). This was followed by an assessment of EGF receptor concentration in the two fractions by quantitative immunoblotting with site-specific antibody to the EGFR as well as the level of tyrosine phosphorylation of the EGFR by *in vivo* labeling with 32 Pi.

Evaluation of Receptor Concentration in PM and Endosome Fractions

Rapid loss of receptor from the PM and rapid concentrative internalization into endosomes was observed (Table I a as described previously [Lai et al., 1989a]) with a 4.3-fold decrease in the concentration of EGFR in PM fractions and an 11-fold increase in receptor concentration in the endosome fraction during 15 min after the injection of EGF.

Phosphotyrosine Content of the EGFR

We next assessed the *in vivo* phosphorylation of the EGFR after sequential injections of 32 Pi and EGF after which specific immunoprecipitation of the EGFR was done on solubilized PM and endosome fractions isolated from the same liver homogenates (Table I b). After the injection of 5 mCi of 32 Pi, the specific radioactivity of hepatic ATP was evaluated by the method of England and Walsh (1976) and found to be constant at 0.74 Ci/mol for 30–75 min after injection. Consequently, 30 min after the injection of 32 Pi, EGF was injected and both PM and GE fractions were isolated from liver homogenates of rats killed at 0, 30 s, 5 and 15 min after injection. The EGFR was immunoprecipitated with mAb IgG 151-BH6 (Lai et al., 1989b) and subjected to SDS-PAGE. Maximum labeling of the receptor (170 kD) in the PM was observed at 30 s after the injection of EGF after which labeling diminished (Fig. 1 A). However, in endosomes, increased labeling was found up to 15 min after EGF injection. Alkali treatment of gels (Fig. 1 B) demonstrated labeling on phosphotyrosine residues for the immunoprecipitated EGFR in PM as well as in endosomes. Densitometry of the X-ray films of immunoprecipitated EGFR after SDS-PAGE and alkali treatment showed that alkali-resistant 32 P-

label in EGFRs remained nearly constant in PM fractions (when expressed per mg cell fraction protein), but increased markedly in endosomes (Table I b). This approach enabled an estimation of the specific radioactivity of the receptor (Table I c). Receptor-specific activity increased significantly in PM between 0 and 30 s after EGF injection but changed little thereafter. However, the specific radioactivity of the EGFR in the GE fraction did not change for the first 30 s after ligand administration despite a twofold increase in receptor concentration (see Table I, a and c). Subsequently, receptor specific activity increased eightfold between 30 s and 5 min after ligand injection and remained constant to 15 min. Of note the specific radioactivity values of the EGFR in endosomes were 2.9- and 2.3-fold higher respectively than the corresponding values for the receptor in PM at 5 and 15 min after injection.

Qualitatively similar findings were observed when experiments were evaluated by immunoblotting with antiphosphotyrosine antibodies. Immunoblotting of total cell fraction protein transferred onto nitrocellulose sheets revealed a major immunoreactive polypeptide at 170 kD whose temporal immunoreactivity in PM and endosomes was similar to that of the 32 P-labeled immunoprecipitated EGFR (see Fig. 1). This was confirmed by immunoprecipitation studies which demonstrated that the major immunoreactive band at 170 kD was indeed the EGFR (Fig. 2 B).

Identification of an EGFR-associated Polypeptide of 55 kD

In the above experiments, a polypeptide of 55 kD was also immunoprecipitated by the EGFR antibody (Figs. 1 and 2). Because 32 P labeling of this protein persisted after alkali treatment of the gels and because it was detected by immunoblotting with phosphotyrosine antibody it is referred to as pyp55. Indeed, in both PM and endosome fractions the pyp55 band was the major antiphosphotyrosine reactive band besides that of the EGFR at 170 kD (Fig. 2). Other immunoreactive bands were observed at 47 and 64 kD (Fig. 2 A). However, these proteins did not coimmunoprecipitate consistently with the EGFR (see Figs. 1 and 2 B).

The immunoprecipitation studies (Figs. 1 and 2) suggested an association of pyp55 with the EGFR which was evaluated by an alternative approach (Fig. 3). Endosomal fractions,

Table I. Ligand-mediated Changes in the Content and Specific Radioactivity of the EGFR in PM and GE Fractions

Time*	a Receptor content No. $\times 10^{-12}$ /mg protein†		b 32 P phosphotyrosine units/mg protein‡		c Specific radioactivity§	
	PM	GE	PM	GE	PM	GE
min						
0	1.59 \pm 0.23	0.30 \pm 0.1	3.2 \pm 1.1	1.0 \pm 0.6	2.0 \pm 0.8	3.3 \pm 2.5
0.5	1.02 \pm 0.36	0.65 \pm 0.16	10.0 \pm 4.2	3.0 \pm 1.0	10.2 \pm 7.1	4.6 \pm 2.0
5	0.52 \pm 0.13	2.13 \pm 0.39	6.6 \pm 2.1	78.4 \pm 16.5	12.6 \pm 4.9	36.8 \pm 10.7†
15	0.37 \pm 0.07	3.28 \pm 0.26	6.2 \pm 0.8	123.3 \pm 10.3	16.7 \pm 4.2	37.6 \pm 4.4**

* Time (min) after the injection of EGF.

† Receptor content (mean $[n = 4] \pm$ SD) was calculated from quantitative immunoblotting as described in Materials and Methods.

‡ 32 P-labeled EGFR was evaluated by densitometry of radioautographs of immunoprecipitated EGFR subjected by SDS-PAGE and alkali-treatment (mean $[n = 3] \pm$ SD).

§ Specific radioactivity, calculated as the ratio of column b/column a.

† Significantly different from the specific radioactivity of the EGFR at 5 min in PM ($P < 0.05$, Student's *t* test).

** Significantly different from value in PM at 15 min ($P < 0.01$).

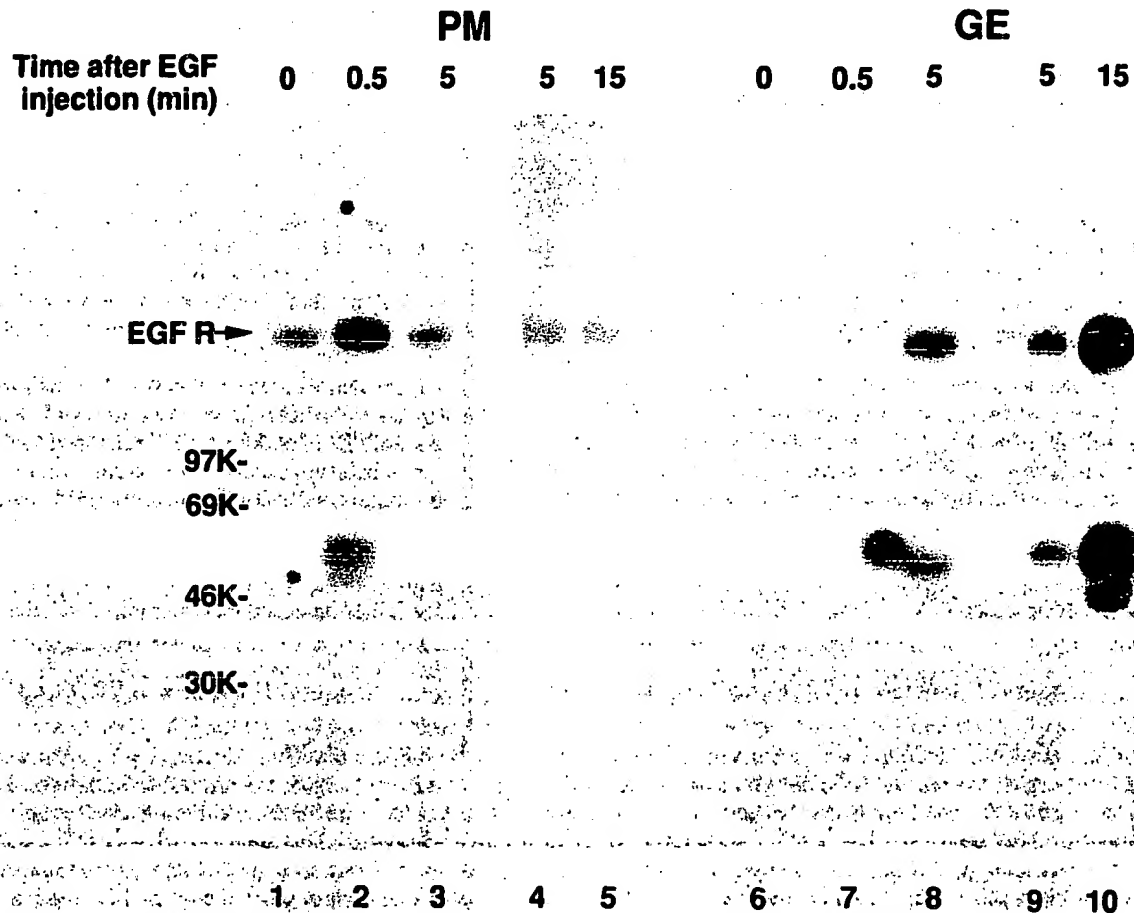
A**Untreated gel**

Figure 1. Immunoprecipitation of in vivo ^{32}P -labeled EGFR. (A and B) EGF was injected at 0, 30 s, and 5 min (experiment I) or at 5 and 15 min (experiment II) into the portal vein of rats that had previously received 5 mCi of ^{32}P orthophosphate. PM and GE fractions were isolated and subjected to immunoprecipitation (PM, 700 μg ; GE, 350 μg protein) followed by SDS-PAGE. All animals were killed at 60 min after injection of ^{32}P orthophosphate. The gels were exposed to X-ray film for 3 d (A; lanes 1-10); then treated with alkali and re-exposed for 10 d (B). The position of the EGFR is indicated by the arrow. As well, in B, the mobilities of the phosphoprotein designated pyp55 and that of a band of molecular mass 47 kD (asterisk) are noted.

isolated 15 min after the injection of EGF, were solubilized and the proteins separated by HPLC gel permeation chromatography. Eluted fractions were electrophoresed, transferred to nitrocellulose sheets, and probed with the antiphosphotyrosine antibody as well as site-specific antibodies to the EGFR. Fractions eluting at a molecular weight of $\sim 440,000$ were reactive with both sets of antibodies. Two major proteins were immunoreactive with antiphosphotyrosine antibodies; one at a molecular mass of 170 kD corresponded to the EGFR as evidenced by immunoblotting with site specific antibodies. The other protein which was immunoreactive with antiphosphotyrosine antibody had a molecular mass identical to pyp55. Whereas the EGFR was found between fractions 8-15, pyp55 was restricted to fractions 8-11 as well as in monomeric form ($\sim 60,000$ in molecular weight [not shown]). This was probably due to dissociation consequent to dilution during chromatography. However, the majority of the EGFR in endosomes was of higher order structure either

in association with pyp55 (fractions 8-11) or with itself (fractions 12-15, $\sim 340,000$ in molecular weight).

Two-dimensional peptide analysis was carried out on the EGFR and pyp55 after solubilization, radiolabeling with Na^{125}I , and immunoprecipitation with anti-EGFR antibody. No overlapping peptides were found (Fig. 4) indicating that pyp55 was a distinct protein. Attempts to generate phosphopeptide maps were unsuccessful due to the low level of ^{32}P incorporation and the lack of sensitivity of antiphosphotyrosine immunoblots after tryptic hydrolysis of the EGFR and pyp55 (data not shown and vide infra, Fig. 5).

Pyp55 did not bind to protein A (data not shown) and therefore was not related to the heavy chain of IgG (expected molecular mass ~ 55 kD). Furthermore, pyp55 was not immunologically related to *src* as mAb MA327 (Lipsich et al., 1983) to pp60^{src} (molecular mass 60 kD) did not immunoprecipitate pyp55 from solubilized endosomes. Neither was the protein related immunologically to the 55-kD tyrosine

B

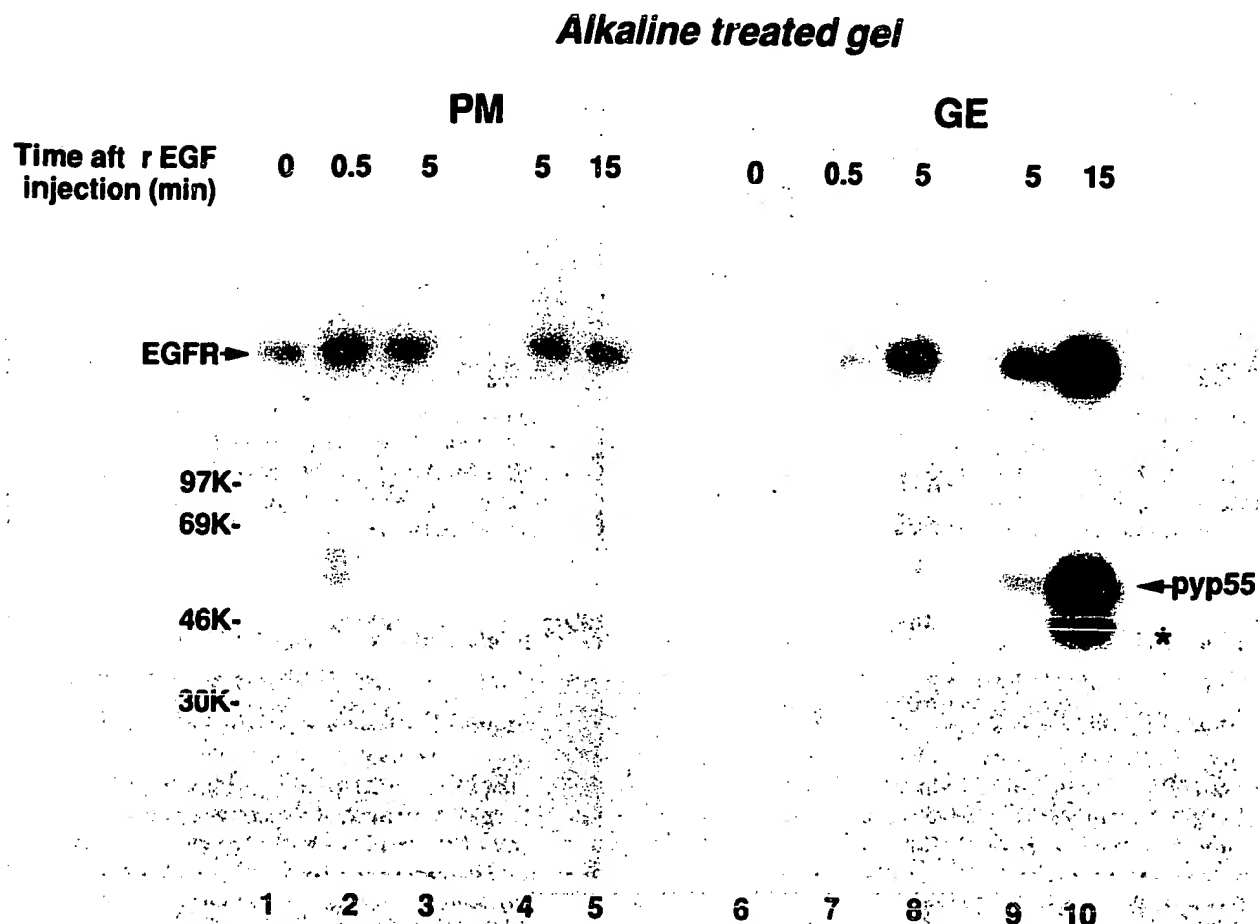


Figure 1.

phosphorylated protein identified by Baribault et al. (1989) since no reactivity was found on immunoblotting with antibodies to this protein with either immunoprecipitates of the EGFR or total endosomal proteins. Finally, phosphorylation of pyp55 was dependent on EGF. The administration of equivalent near saturating doses of insulin (15 μ g/100 g bw) led to the endosomal accumulation of insulin receptors to levels similar to those of the EGFR shown in Table I. However, no association of pyp55 with the insulin receptor was found after immunoprecipitation nor was pyp55 phosphorylated after insulin administration as evaluated by Western blotting with antiphosphotyrosine antibody.

Orientation and Localization of the In Vivo Labeled EGFR in Endosomes

Isolated endosomes were subjected to limited proteolysis to evaluate the orientation of the EGFR and pyp55 in endosomes. Endosomes isolated 15 min after the injection of EGF were treated with increasing concentrations of trypsin at 0°C followed by immunoblotting with antiphosphotyrosine antibody. At the lowest dose of trypsin employed (0.4 μ g/ml), immunoreactivity (with antiphosphotyrosine antibody) of the 170-kD EGFR as well as pyp55 was greatly diminished (Fig. 5 A; quantified in Fig. 5 B). Similar observations were found using site-specific antibody to the

carboxyl-terminal tail of the EGFR (data not shown). By contrast, [125 I]EGF internalized into the same endosomes was insensitive to this limited protease digestion in the absence but not the presence of detergent (Fig. 5 B). Experiments were attempted to immunolocalize directly antiphosphotyrosine antibodies on isolated endosomes by the protein-A gold technique as described by Dominguez et al. (1991). These were, however, without success presumably due to the low signal (vide infra).

Discussion

Our studies and those of others (Dunn and Hubbard, 1986; Kay et al., 1986; Lai et al., 1989a) have demonstrated that after EGF administration, the EGFR is rapidly internalized into hepatic endosomes. We also found that the majority of endosomal ligand (EGF) remains receptor bound even 15 min after the injection of EGF (Lai et al., 1989b). The present study was undertaken to evaluate the phosphotyrosine content of the EGFR in isolated endosomes with comparison to what was observed at the cell surface.

The radioactivity in the 32 P-phosphotyrosine-labeled receptor was estimated by immunoprecipitating EGFR after the intraportal injection of 32 Pi. Accurate determination of EGFR concentration in the subcellular fractions was achieved by quantitative immunoblotting (see also Lai et al., 1989a).

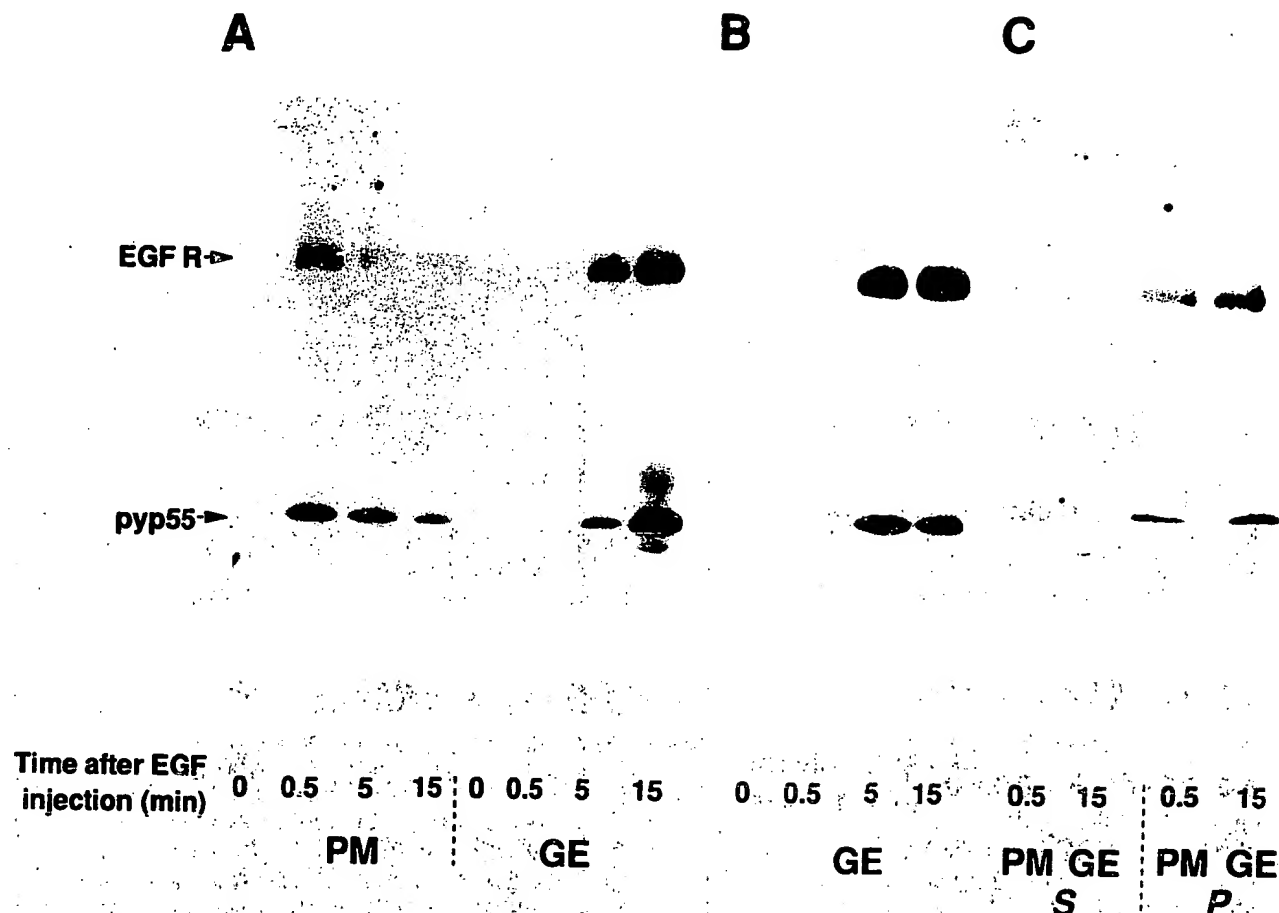


Figure 2. Immunoblot analysis of EGFR and substrates by anti-phosphotyrosine antibody. Membrane fractions (50 μ g) of PM (lanes 1–4) and GE (lanes 5–8) were isolated from rats sacrificed at 0, 0.5, 5, and 15 min after the injection of EGF. (A) The fractions were subjected to SDS-PAGE and immunoblotted with antiphosphotyrosine antibody as described in Materials and Methods. (B) Endosomes (GE, 50 μ g protein) were solubilized and after incubation with EGFR antibody, the immunoprecipitate was subjected to SDS-PAGE followed by immunoblotting with antiphosphotyrosine antibody. At 15 min after the injection of EGF additional bands at 47 and 64 kD are observed in addition to the EGFR and pyp55. (C) GE and PM fractions (100 μ g protein each) isolated at 0.5 and 15 min after the injection of EGF were incubated with 0.1 M sodium carbonate on ice for 30 min followed by centrifugation at 200,000 g for 30 min. The supernatants (S) and pellets (P) were subjected to SDS-PAGE followed by immunoblotting with antiphosphotyrosine antibody. The positions corresponding to the molecular masses of the EGFR and pyp55 are indicated.

using a site-specific antibody to the EGFR. 32 P-phosphotyrosine content per unit receptor (i.e., specific radioactivity) was then calculated from the densitometry of 32 P-labeled immunoprecipitated EGFR divided by the receptor content. The data clearly establish that ligand-dependent tyrosine phosphorylation was initiated at the cell surface with a five-fold increase in receptor-specific activity observed in plasma membranes within 30 sec after the administration of EGF. Endosomal receptor specific activity was significantly greater than that of PM-receptors at either 5 ($P < 0.05$) or 15 min ($P < 0.01$) after injection. However, when calculated as the fold increase in specific activity over that at zero time, receptor-specific activity in endosomes at 15 min was only slightly greater (11.4-fold increase) than that calculated for PM over the same time interval (8.4-fold increase). (This discrepancy was due to the high variation in the estimation of

the low receptor concentration and low 32 P-labeling of the EGFR in the GE fraction at zero time (Table I c)). Though consistent with the view that receptor phosphorylation was enhanced in endosomes our data do not exclude the possibility that receptor phosphorylation occurred only in the PM with highly phosphorylated receptors being preferentially internalized. On the other hand, within the first 30 s after EGF injection PM receptor specific activity increased five-fold whereas endosomal receptor specific activity remained similar to the low zero time level despite a twofold increase in receptor concentration in endosomes. Here there would appear to have been selective internalization of only poorly phosphorylated cell surface EGFRs. Thus the hypothesis of selective internalization appears to be a rather more complicated explanation for our data.

The yield of the PM fraction was ~14% based on the

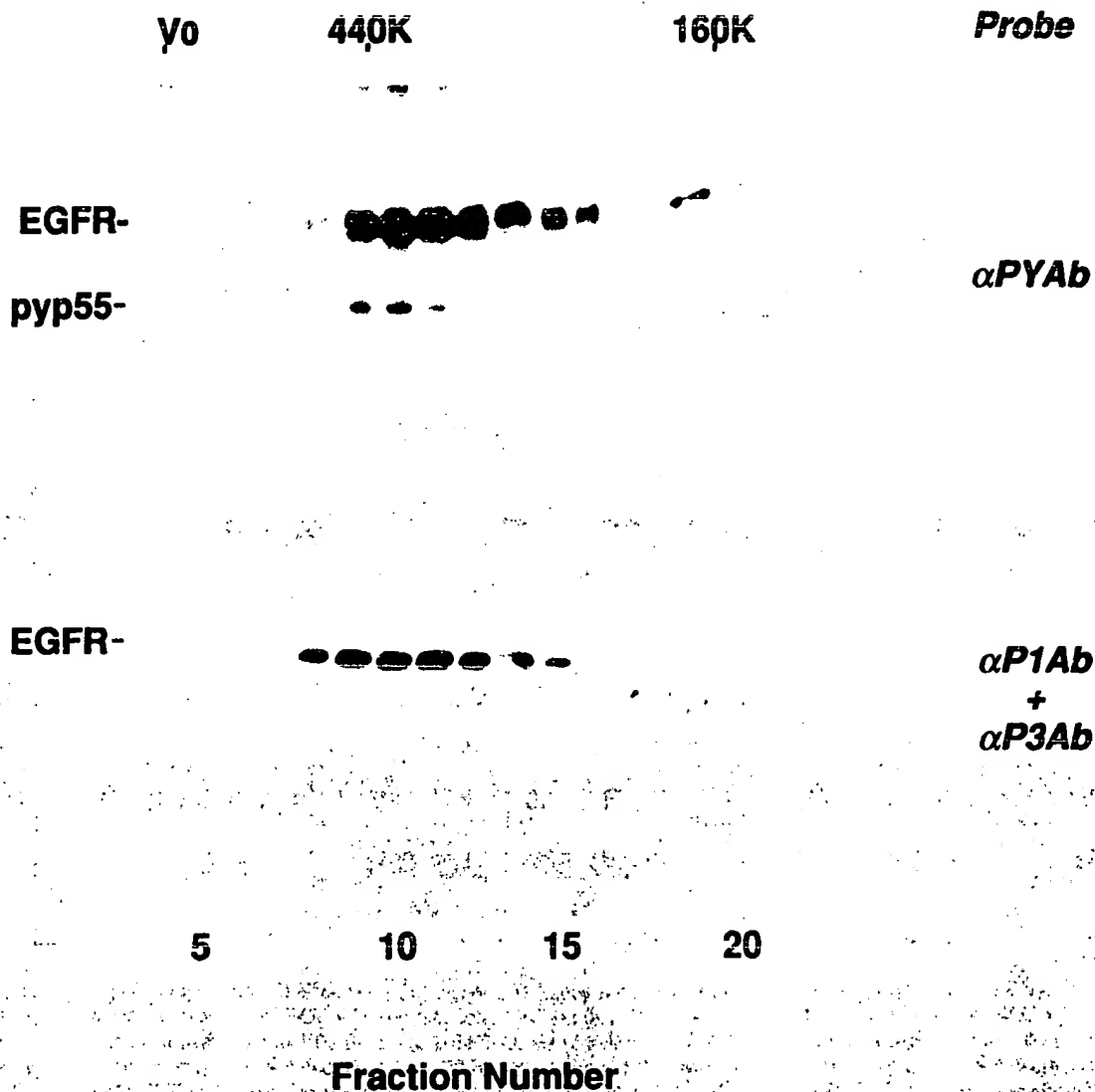


Figure 3. Coelution of pyp55 with EGFR in gel permeation chromatography. GE fractions (250 μ g protein) isolated 15 min after the injection of EGF (10 μ g/100 g bw) were solubilized as described in Materials and Methods. Eluted fractions were subjected to immunoblotting with the anti-phosphotyrosine antibody (*upper panel*) or a mixture of site-specific antibodies against synthetic peptides corresponding to residues 1,164–1,176 (α P1Ab) and 1,059–1,072 (α P3Ab) of the EGFR. Vo, void volume; 440 K, elution position of ferritin; 160 K, elution position of γ -globulin. On the left is indicated the positions of the EGFR and pyp55.

receptor content of these fractions compared to that of a total particulate fraction (Lai et al., 1989a). The yield of endosomes was $\sim 32\%$ (calculated from the receptor content in endosomes at 15 min after injection of saturating levels of EGF (Table I of the present study and Lai et al., 1989a) as compared to that of total particulate fractions of liver homogenates (Lai et al., 1989a). EM of the PM fraction indicated a representative cell fraction consisting of all domains (sinusoidal, lateral, bile canalicular) of the hepatic cell surface (Hubbard et al., 1983; Lai et al., 1989a). This was not the case for the endosomal fraction. The endosomal components of the GE fraction consisted mainly of tubulovesicular profiles with the vesicular components of ~ 250 –300 nm in diameter containing intraluminal lipoprotein-like particles (Lai et al., 1989b; Dhermy et al., 1990). The much

larger (and denser) multivesicular bodies were not found in this fraction. Indeed, the studies employing limited proteolysis of the GE fraction (Fig. 5) demonstrated that the tyrosine phosphorylated domain of the EGFR was cytosolically oriented while internalized [125 I]EGF was intraluminal. Taken together with past studies showing that at this dose of injected ligand and at 15 min after injection, [125 I]EGF was largely receptor bound and localized to the bounding membrane of endosomes (Lai et al., 1989b), we conclude that little if any of internalized EGF or tyrosine-phosphorylated EGFR was sequestered within intraluminal vesicles of multivesicular bodies in the GE fraction. Other investigators have clearly demonstrated internalized EGFR within such structures (McKanna et al., 1979; Hopkins, 1990; McCune et al., 1990). It is, however, noteworthy that Carpentier et

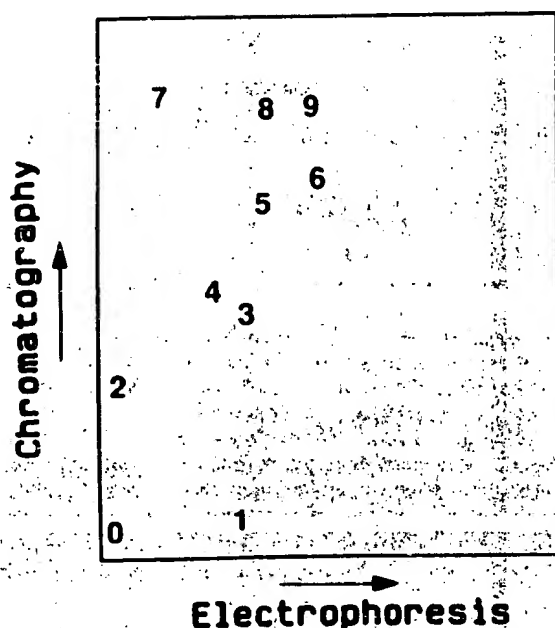
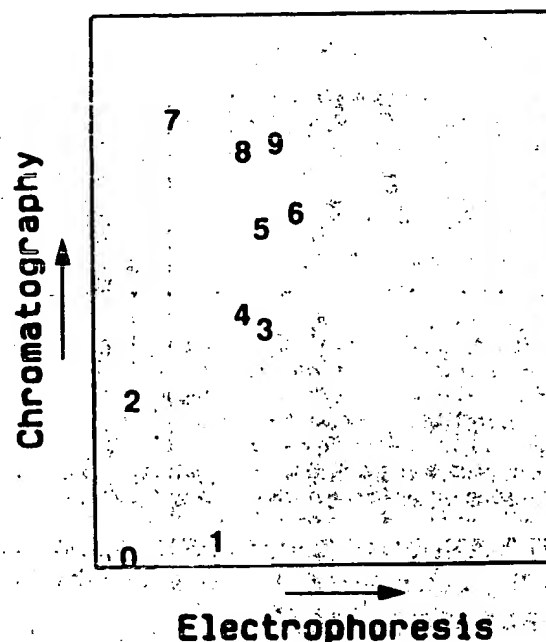
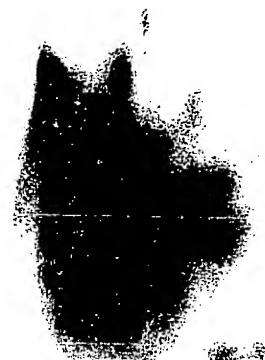
A**B**

Figure 4. Two dimensional peptide maps of EGFR (A) and pyp55 (B). GE fractions were isolated at 15 min after the injection of EGF. The fractions were solubilized, dephosphorylated, and iodinated with Na¹²⁵I as described in Materials and Methods. After immunoprecipitation with mAb to the EGFR, the radioiodinated EGFR and pyp55 were resolved by nonreducing SDS-PAGE, extracted from the gel, and digested with TPCK trypsin. Resulting peptides were applied onto a cellulose plate equilibrated with 30% formic acid and the [¹²⁵I] labeled tryptic peptides were resolved electrophoretically in 30% formic acid, then by chromatography in *n*-butanol/acetic acid/pyridine/H₂O (60:12:40:48). The plates were stained with ninhydrin and were exposed to X-ray film. In each case, the origin is indicated (o). None of the major [¹²⁵I] peptides of the EGFR (A) corresponded to those of pyp55 (B). The numbers indicate the locations of the ninhydrin positive spots which were due to degraded fragments of trypsin and used to align the two maps.

al. (1987) have immunolocalized phosphotyrosine to the cytosolic surface of endosomes in A431 cells after the administration of EGF. Even so, A431 cells have been reported by Wiley et al. (1988) to be defective in internalization of the EGFR. Hence, the studies of Carpentier et al. (1987) may have underestimated the significance of phosphotyrosine labeling in endosomes. A431 cells have been reported to

have ca. 2×10^5 receptors per cell (Haigler et al., 1979; Krupp et al., 1982; Garnou et al., 1984). The much larger hepatocyte has less than 10^5 receptors per cell (Lai et al., 1989a). It was perhaps not surprising therefore that our own attempts to visualize phosphotyrosine labeling in endosomes by EM immunolabeling were unsuccessful (not shown).

In vivo labeling of the EGFR was determined after immu-

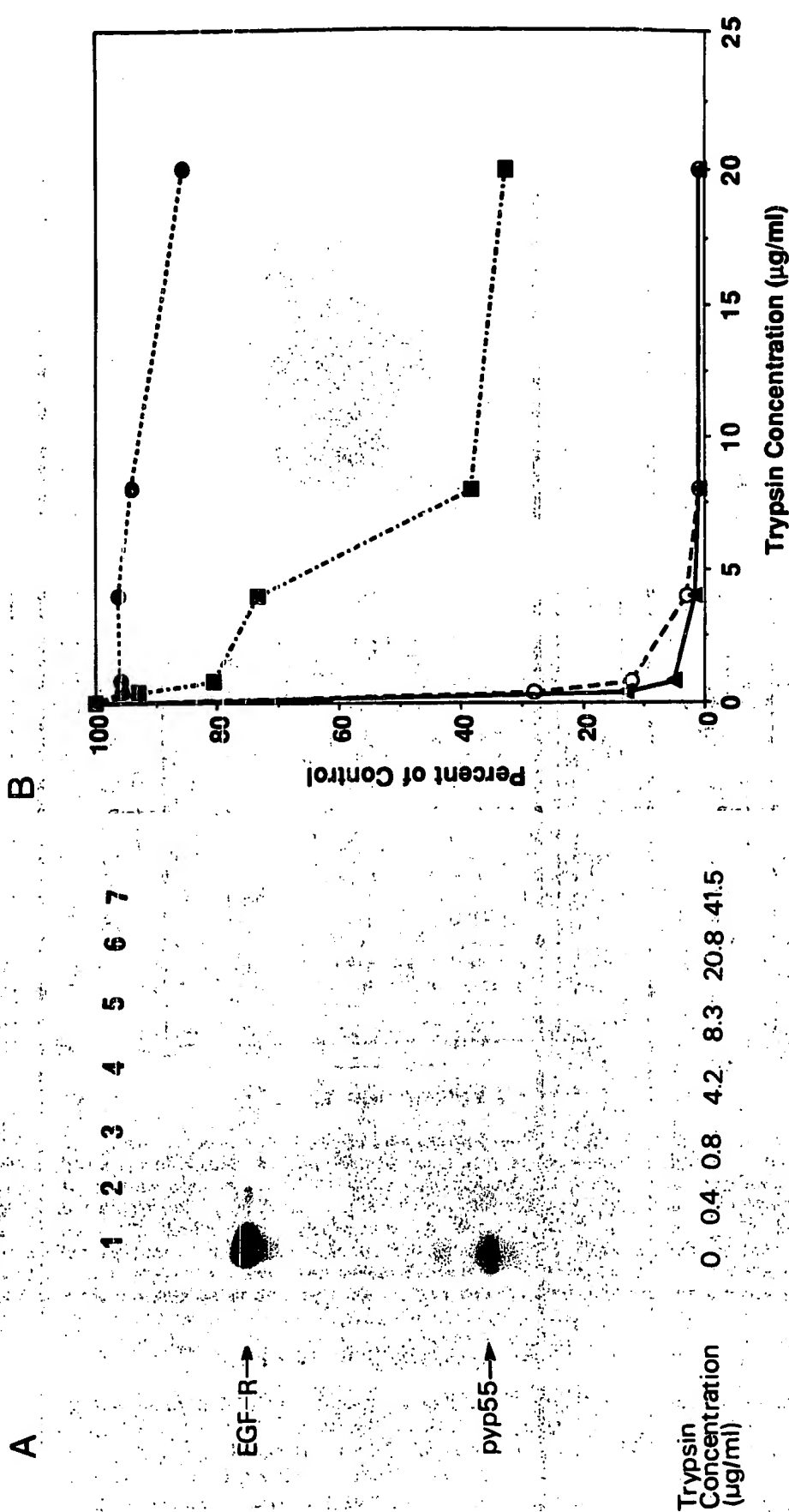


Figure 5. Orientation and localization in intact endosomes of the in vivo phosphorylated EGF-R and pyp55. GE fractions were isolated 15 min after the injection of unlabeled EGF (10 µg/100 g bw). The fractions (15 µg membrane protein) were incubated with increasing concentrations of trypsin as described in Materials and Methods, then electrophoresed by SDS-PAGE. The proteins transferred to nitrocellulose sheets and probed with antiphosphotyrosine antibodies (A). The proportion of phosphotyrosine reactive EGF-R (170 kD) (O---O) and pyp55 (55 kD) (▲---▲) were then estimated by densitometry (B). The proportion of protease sensitive internalized [¹²⁵I]EGF in endosomes was determined on concurrent experiments carried out in the presence (■---■) or absence (●---●) of Triton X-100.

noprecipitation with a mAb to the EGFR. Coprecipitating with the EGFR was an associated phosphotyrosine-labeled protein (pyp55) whose tyrosine phosphorylation was EGF dependent. Pyp55 was also readily seen in immunoblotting PM and endosome fractions with antiphosphotyrosine antibodies. It was concluded that the protein was specifically associated with the EGFR in endosomes on the basis of its coprecipitation as well as by its demonstrated association during HPLC gel permeation chromatography of solubilized endosomes. The molecular weight of the EGFR:pyp55 complex was estimated by gel permeation chromatography to be ~440,000 which would be consistent with 2 mol of the EGFR and 2 mol of pyp55. The phosphoprotein pyp55 was found in association with the EGFR at initial times of activation at the cell surface, i.e., at 30 s as well as at peak times of internalization in endosomes (5–15 min). It was not possible to identify by Coomassie blue staining the amount of this protein in immunoprecipitates since it was below the limit of detection.

From their studies on the regulation of recycling of the Fc receptor, Mellman et al. (1984) have proposed that conditions favoring Fc receptor oligomerization would lead to downregulation while conditions favoring receptor monomer formation would lead to receptor recycling. The studies of Honegger et al. (1987) and Felder et al. (1990) have suggested that the tyrosine kinase activity of the EGFR in endosomes may be necessary for downregulation. Since our experimental conditions (EGF dose of 10 μ g/100 g bw) favored downregulation (Lai et al., 1989a) we suggest that a possible function of pyp55 is to regulate the oligomerization of the EGFR in endosomes in a tyrosine phosphorylation dependent manner thereby regulating receptor downregulation. Current experiments aimed at purifying pyp55 and determining its primary structure by cDNA cloning could help elucidate the significance of this EGFR-associated phosphoprotein.

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